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Haslam et al.

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[54] **OPHTHALMIC DRUG DELIVERY SYSTEM UTILIZING THERMOSETTING GELS**

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[52] **U.S. Cl.** .... **424/78;** 424/85; 424/94; 424/114; 424/116; 424/177; 424/180; 424/181; 424/209; 424/211; 424/220; 424/221; 424/224; 424/230; 424/238; 424/243; 424/246; 424/248.51; 424/251; 424/253; 424/254; 424/256; 424/258; 424/263; 424/265; 424/267; 424/270; 424/271; 424/273 P; 424/273 R; 424/274; 424/275; 424/283

[58] **Field of Search** .... 424/85, 94, 114, 116, 424/177, 180, 181, 209, 211, 220, 221, 224, 230, 238, 243, 246, 248.51, 251, 253, 254, 256, 258, 263, 265, 267, 270, 271, 273 P, 273 R, 313, 317, 321, 322, 324, 326, 330, 343, 274, 275, 283, 285, 300, 309, 311

[56] **References Cited**

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3,711,604	1/1973	Colodney et al.	424/78
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4,188,373	2/1980	Kresanski	424/177

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1072413	7/1976	Canada .

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Journal of Pharm. & Pharmacology-"Novel Poloxamer & Poloxamine Hydrogels: Swelling & Drug Release" vol. 32, p. 5p, (1980), by A. Saden, A. J. Florence, T. L. Whateley.

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[57] **ABSTRACT**

This invention describes the application of selected polymers as novel drug delivery systems which use the body temperature and pH to induce a liquid to gel transition of the polymer which contains a drug or therapeutic agent therein. The goal of such a delivery system is to achieve a greater degree of bioavailability or sustained concentration of a drug.

54 Claims, 2 Drawing Figures

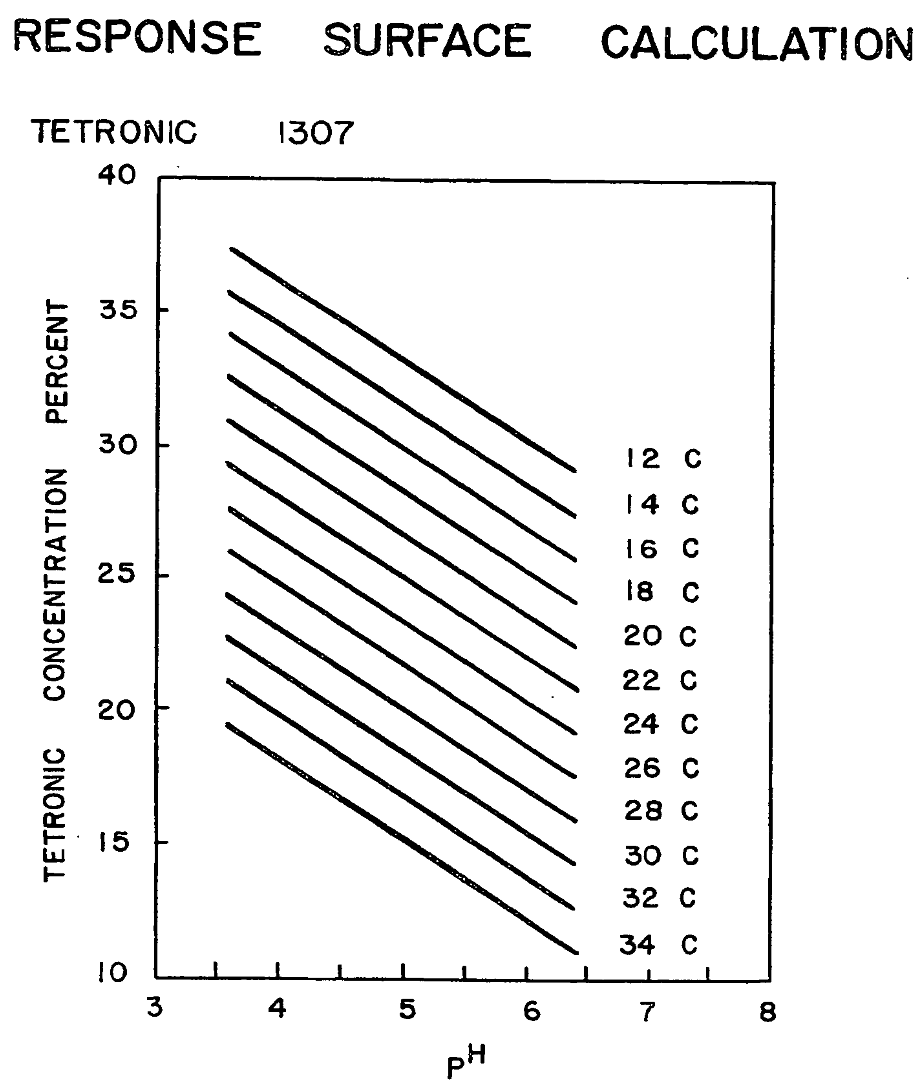

RESPONSE SURFACE CALCULATION
TETRONIC 1307
TETRONIC CONCENTRATION PERCENT
40
35
30
25
20
15
10
3
4
5
6
7
8
PH
12 C
14 C
16 C
18 C
20 C
22 C
24 C
26 C
28 C
30 C
32 C
34 C

Fig. 1

A PLOT OF THE FLUID CONCENTRATION (MOLAR) OF TIMOLOL AS A FUNCTION OF TIME (MINUTES) IN THE RABBIT FOLLOWING INSTILLATION OF 25 MICROLITER VOLUMES OF THE FOLLOWING FORMULATIONS:

◆ 27% TETRONIC THERMAL GEL 1307; pH4
■ 22% TETRONIC THERMAL GEL 1307; pH4
● TIMOPTIC 0.5% pH 6.8 (COMMERCIALLY AVAILABLE)

EACH OF THE FORMULATIONS CONTAINED A 0.5% TIMOLOL BASE EQUIVALENT.

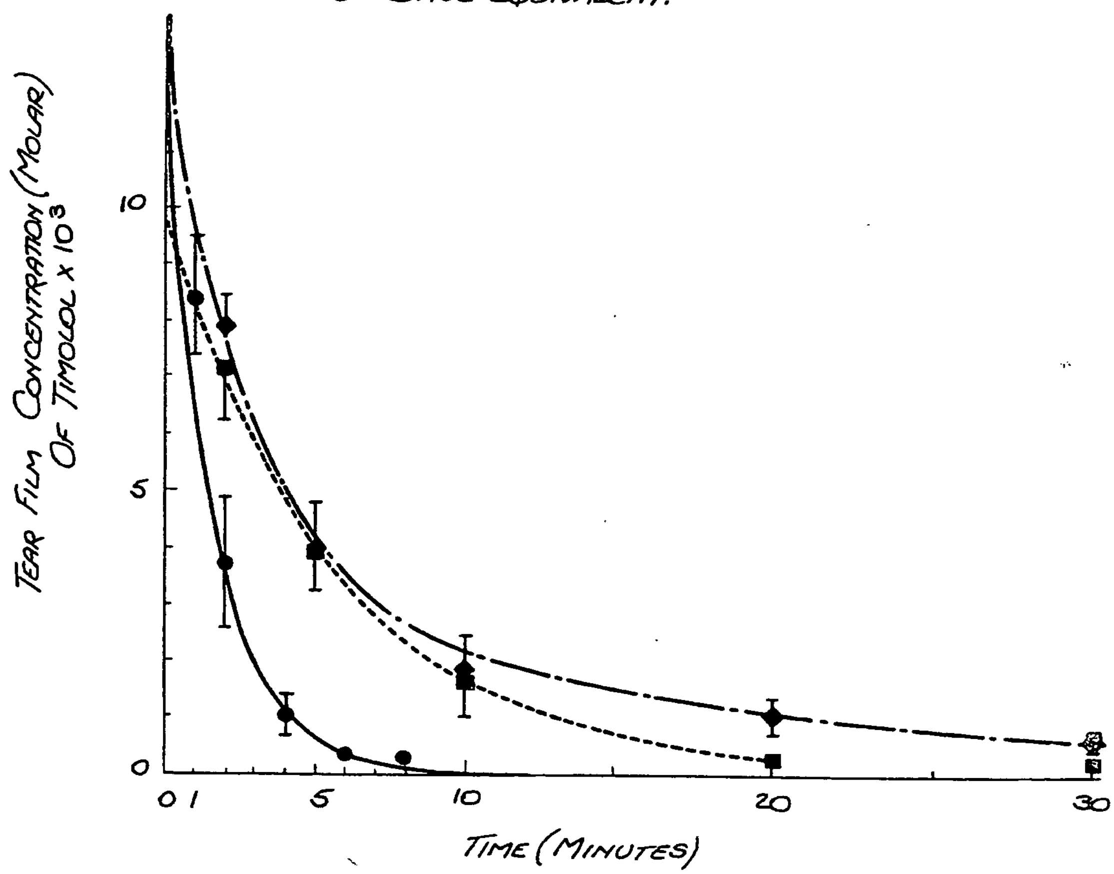


Fig. 2.

OPHTHALMIC DRUG DELIVERY SYSTEM UTILIZING THERMOSETTING GELS

BACKGROUND OF THE INVENTION

A major loss of drugs administered to the eye is via the lacrimal drainage system so that only a small fraction of the dose remains in the eye for an extended period of time from a liquid drop formulation.

Different approaches have been taken to slow down this rapid loss of drug by using viscous solutions, gels, ointments and solid inserts.

Improvement in drug delivery has been achieved by these methods especially with the use of solid inserts where a large reduction in dose is possible while achieving the same therapeutic response as a liquid drop which must be administered more frequently and at higher drug concentration.

A principal advantage of the present invention is that it permits the accurate, reproducible unit dosing of a drug or active entity by using volumetric fluid delivery of the dosage prescribed while effecting the ultimate delivery of a semi-solid or rigid gel state. Conventionally, it is not possible to deliver preformed gels from multiple dose containers readily by volumetric means. Gravimetric dosing is thus required to achieve uniform content in delivering reproducible quantities. Conventionally, voids and packing or consolidation problems result when administering semi-solid preparations volumetrically. The present invention provides extremely accurate and uniform content of dose which is critical for many potent drugs.

A significant disadvantage to a solid insert however is that many patients have a difficult time inserting a solid object into the cul-de-sac of the eye and removing said solid object.

Another approach to these problems is to use a formulation which is a liquid at room temperature but which forms a semi-solid when warmed to body temperatures. Such a system has been described in U.S. Pat. No. 4,188,373 using "Pluronic® polyols" as the thermally gelling polymer. In this system the concentration of polymer is adjusted to give the desired sol-gel transition temperature, that is lower concentration of polymer gives a higher solution-gel (sol-gel) transition temperature. However, with the currently commercially available "Pluronic®" polymers the ability to obtain a gel of the desired rigidity is limited while maintaining the desired sol-gel transition temperature at physiologically useful temperature ranges near 26°-35° C.

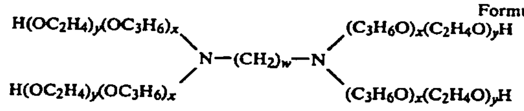
Similarly Canadian patent 1072413 which relates to (poloxamer) gel systems with gelling temperatures higher than room temperature uses additives to bring about the gelling characteristics of the polymer which contains therapeutic or other type agents. Also in this Canadian patent "Tetronic®" polymers are used as additive agents rather than the primary polymeric agent as in the instant case.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical vehicle which is useful in delivering pharmacologically active medicaments to the eye and in some cases as in dry eye using the vehicle alone. The drug delivery system consists of a clear physiologically-acceptable liquid which forms a semi-solid "gel" at human body temperatures. The sol-gel transition temperature and rigidity of the gel can be modified by changes in polymer concentration combined with the pH and ionic strength of the solution.

It has been discovered that certain polymers are useful vehicles having the properties set forth above. The polymers are tetra substituted derivatives of ethylene diamine (poloxamine, w=2 in Formula I), propylene diamine (w=3), butylene diamine (w=4), pentylene diamine (w=5) or hexylene diamine (w=6). The substituents are block copolymers of poly(oxypropylene) and poly(oxyethylene) of various chain lengths and ratios x to y in the general formula of the polymer shown below.

Formula I



wherein w is an integer from 2 through 6.

A typical polymer system of our invention would contain a polymer containing approximately 40 to 80% poly(oxyetnylene) and approximately 20 to 60% poly(oxypropylene). The total molecular weight of the polymer used in our invention is at a minimum about 7,000 and can go as high as 50,000 but preferably is in the range of 7,000 to 30,000; and x and y are any integers within the above constraints. Preferred polymers are those of the formula above where w=2, namely the poloxamine polymer.

The aqueous drug delivery vehicle would contain from 10% to 50% by weight of the entire vehicle as polymer described above. The aqueous drug delivery vehicle would also contain the drug or therapeutic agent in addition to various additives such as acids or bases to adjust the pH of the composition, buffers to maintain the pH, preservatives to control bacterial contamination, other additives to provide for drug solubility and stability and formulation performance with purified water making up the remainder of the drug delivery vehicle.

DETAILED DESCRIPTION OF THE INVENTION

The invention consists of a pharmaceutical composition or drug delivery system which is a clear physiological acceptable solution at room temperature or lower but which forms a semi-solid or gel when placed in the eye. The unique feature of this system is that both the gel transition temperature and/or the rigidity of the gel can be modified by adjustment of the pH and or ionic strength and polymer concentration.

The ability to change the sol-gel transition temperature by pH adjustment is a critical feature of the invention which overcomes many of the disadvantages of previous approaches. Also the sol-gel transition temperature can be modified somewhat by ionic strength adjustment.

An example of a drug delivery vehicle in accordance with this invention consists of an aqueous solution of, for example, a tetra substituted ethylene diamine block copolymer of poly(oxyethylene)-poly(oxypropylene) (where w=2 in Formula I) in which the substitution at the nitrogen is to the poly(oxypropylene) block and the polymer consists of about 40-80% as the poly(oxyethylene) unit and about 20-60% as the polypropylene unit and which has a total average molecular weight of 7,000

to 50,000 with a preferred range of 7,000-30,000. Such polymers are included in the polymers sold under the trademark "Tetronic®" polyols by BASF Wyandotte Corporation.

Other polymers where w=3 to 6 (of Formula I) can be made according to methods known in the art (Block and Graft Copolymerization, Vol. 2 edited by R. J. Ceresa published by John Wiley and Sons, 1976) by using the appropriate initiators such as for example propylenediamine, butylenediamine, pentylenediamine and hexylenediamine.

The preferred polymers are those which form gels at a concentration range of 10 to 50% of the polymer to water.

A good example of a typical polymer used in the drug delivery system of our invention is Tetronic® 1307 which thermally gels over a concentration range of about 15% to 35% in water with gelling temperatures of about 30° C. to 10° C. at neutral pH. The gel strength at 35% concentration is much more rigid than at the 15% gel concentration. However, with a solution-gel transition temperature of about 10° C. for the 35% solution any useful liquid product would have to be refrigerated below this temperature. A useful vehicle can be prepared however by modification of both concentration and pH. For example a 27% Tetronic® 1307 solution at neutral pH has a gel-sol transition temperature of about 16° C. but at pH 4 (adjusted to such with HCl at 10° C.) the transition temperature is about 25° C. The gel formed under these conditions meets the requirements of a fairly rigid gel which is a liquid at room temperature.

The effect of pH and polymer concentration on gelling temperature for Tetronic® 1307 is shown in FIG. 1. Thus, for example, at a concentration of polymer to water of 25% the gelling temperature is 19° C. at pH 6 and increases to 26° C. at pH 4.

For administration of the drug delivery system of our invention to the eye as drops, the pH of the system can range from 2 to 9 with the preferred pH range being 4 to 8. The pH, concentration and gelling temperatures will vary for any individual polymer falling within the class covered in this invention and these factors can be determined by those skilled in the art in possession of this concept.

The pH of the drug delivery system is adjusted by adding the appropriate amount of a pharmaceutically acceptable acid or base to obtain the required pH. The acid or base can be any that are known to persons skilled in the art but are preferably hydrochloric acid or sodium hydroxide.

In general the ophthalmic drug delivery vehicle of the present invention will contain from about 0.01 to about 5% of the medicament or pharmaceutical, from about 10% to about 50% of the polymer and from 90% to about 45% water. In special situations, however, the amounts may be varied to increase or decrease the dosage schedule.

If desired, the drug delivery vehicle may also contain, in addition to the medicament, buffering agents and preservatives. Suitable water soluble preservatives which may be employed in the drug delivery vehicle are sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzyl alcohol and phenylethanol. These agents may be present in amounts of from 0.001 to 5% by weight and preferably 0.01 to 2%. Suitable water soluble buffering agents are alkali or alkali earth carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and the like, such as sodium phosphate, citrate, borate, acetate, bicarbonate and carbonate. These agents may be present in amounts sufficient to maintain a pH of the system of between 2 to 9 and preferably 4 to 8. As such the buffering agent can be as much as 5% on a weight to weight basis of the total composition.

Another factor which can affect the gelling temperature of the drug delivery vehicle or pharmaceutical composition is its ionic strength and this can be varied by adding to the drug delivery vehicle a pharmaceutically acceptable salt, such as sodium chloride, potassium chloride or mixtures thereof or even suitable alkali metal salts such as sodium sulfate and the like. The effect of adding sodium chloride is to decrease the gelling temperature by about 3° C. for a change of 0.2 molar in ionic strength. Fortunately for a typical ophthalmic dosage the pH and ionic strength effects will help maintain the drug delivery system as a gel in the eye. For example, a 27% thermally gelling solution (thermogel) at pH 4 and low ionic strength (about 0) when in the eye will be bathed with pH 7.4 and isotonic lacrimal fluid which at the surface of the gel will act to lower the gel-sol transition temperature thus helping to maintain and insure a gelled formulation in the eye rather than having the drug delivery system liquefy and perhaps be eliminated rapidly from the eye through the lacrimal drainage system.

A unique aspect of the gel which is formed in situ in the eye or preferably in the inferior cul-de-sac of the eye is its prolonged residence time compared to conventional ophthalmic solutions. The tear turnover usually dilutes and depletes the drug reservoir very rapidly in conventional solutions. The thermogel formulation dissolves more slowly and promotes an enhanced delivery of the dissolved or dispersed agent within it. This prolonged residence time leads to more effective levels of concentration of agent in the tear film. An example of this longer residence time of the drug in the tear film is shown in FIG. 2. The two thermogel formulations show a higher concentration of timolol for an extended period of time than the conventional marketed product. A dose sparing effect on the total amount of drug or agent applied and greater therapeutic effectiveness can be achieved with the thermogel formulations due to higher concentration of agent in the tear film when the agent penetrates the eye if this is desired or within the tear film if penetration is not desired.

Any pharmaceutically active material or diagnostic agent may be delivered in the drug delivery system of this invention. Preferably the drug or pharmaceutical is water soluble although some drugs will show greater solubility in the polymer system than others. Also the drugs or diagnostic agents can be suspended in the polymer vehicle.

Suitable drugs or diagnostic agents which can be administered by the drug polymer delivery system of the present invention that might be mentioned are:

(1) antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoyl-thienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin, sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; naladixic acid and ana-

logs such as norfloxacin and the antimicrobial combination of fluealanine/pentizidone; nitrofurazones, and the like;

(2) antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline, and the like;

(3) anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, fluocortolone, prednisolone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac, its salts and its corresponding sulfide, and the like;

(4) miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivolyl epinephrine, neostigmine, echothiopate iodide, demecarium bromide, carbachol, methacholine, bethanechol, and the like;

(5) mydriatics such as atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine, and the like; and other medicaments used in the treatment of eye conditions or diseases such as

(6) antiglaucoma drugs for example, timolol, especially as the maleate salt and R-timolol and a combination of timolol or R-timolol with pilocarpine. Also included are: epinephrine and epinephrine complex or prodrugs such as the bitartrate, borate, hydrochloride and dipivefrin derivatives and hyperosmotic agents such as glycerol, mannitol and urea;

(7) antiparasitic compounds and/or anti-protozoal compounds such as ivermectin; pyrimethamine, trisulfapyrimidine, clindamycin and corticosteroid preparations;

(8) antiviral effective compounds such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, and interferon and interferon inducing agents such as Poly I:C;

(9) carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)thio-5-thiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide and 6-pivaloyloxy-2-benzothiazolesulfonamide;

(10) anti-fungal agents such as amphotericin B, nystatin, flucytosine, natamycin, and miconazole;

(11) anesthetic agents such as etidocaine cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine;

(12) ophthalmic diagnostic agents such as

(a) those used to examine the retina and choride-sodium fluorescein;

(b) those used to examine the conjunctiva, cornea and lacrimal apparatus such as fluorescein and rose bengal; and

(c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine;

(13) ophthalmic agents used as adjuncts in surgery such as alpha-chymotrypsin, and hyaluronidase;

(14) chelating agents such as ethylenediamine tetraacetate (EDTA) and deferoxamine;

(15) immunosuppressive agents and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine, and azathioprine; and

(16) combinations of the above such as antibiotic/anti-inflammatory as in neomycin sulfate-dexamethasone sodium phosphate, concomitant antiglaucoma therapy such as timolol maleate-aceclidine.

Typically as stated previously, the present liquid drug delivery device would contain from about 0.001 to about 5% of the medicament or pharmaceutical on a weight to weight basis. Thus, from one drop of the liquid composition which contains about 25 mg of solution, one would obtain about 0.0025 mg to about 1.25 mg of drug.

The particular drug or medicament used in the pharmaceutical composition of this invention is the type which a patent would require for pharmacological treatment of the condition from which said patient is suffering. For example, if the patient is suffering from glaucoma, the drug of choice would probably be timolol.

Also included in this invention is the use of the drug delivery device or pharmaceutical composition minus the active drug or medicament for the treatment of dry eye. All the ratios of components as described above would be satisfactory for the composition used for dry eye. For this use, one would administer drops as needed.

The preparation of the drug delivery systems are described below and the appropriate examples which follow were all carried out according to this procedure. Since the polymer systems of this invention dissolve better at reduced temperatures, the preferred methods of solubilization are to add the required amount of polymer to the amount of water to be used. Generally, after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostated container at about 0° C. to 10° C. to dissolve the polymer. The mixture can be stirred or shaken to bring about a more rapid solution of the polymer.

The drug substance or medicaments and various additives such as buffers, salts and preservatives are then added and dissolved. The final desired pH adjustment can be made by adding the appropriate acids or bases such as hydrochloric acid or sodium hydroxide to the drug delivery system.

When used in the eye the pharmaceutical composition will be administered as a fluid by any conventional means of delivering drop formulations to the eye such as by means of an eye-dropper or by using an Ocumeter®. Typically these formulations are intended to be administered into the inferior cul-de-sac of the eye. This can easily be accomplished by distending the lower lid from the eye and applying the drop within the sac and then releasing the lid.

EXAMPLES

The following examples are illustrations and are not intended to be restrictive of the scope of the invention.

All percentages are given in (w/w) % and all pH measurements are for 10° C. In the animal experiments, 25 mg of each solution was administered to tne inferior cul-de-sac of the eye.

EXAMPLE 1

The use of the polymer vehicle to deliver pilocarpine.

	Solution 1	Solution 2	Solution 3
Pilocarpine	0.5%	0.1%	0.5%
Tetronic 1307	27.0%	27.0%	—
pH adjusted with HCl to	4.0	4.0	4.0
sufficient purified water to make	100%	100%	100%
gel-sol transition temp.	26° C.	26° C.	—

Pilocarpine is known to produce a miotic effect (constriction of the iris). In an experiment in rabbits the miotic effect of pilocarpine in the thermally gelling solutions 1and 2 was compared with solution 3, a conventional liquid drop. The pupillary diameter change was measured over 3 hours. The results showed solution 1 had a larger area under the curve than 2 or 3 and that solutions 2 and 3 had about the same AUC. The relative area under the curve measurements:

Solution	Relative AUC
1	1.3
2	0.9
3	1.0

These results indicate about a 5-fold reduction in pilocarpine concentration in the thermally gelling solution (solution 2) can produce a similar pharmacological response as a conventional drop (solution 3).

EXAMPLE 2

The use of the polymer vehicle to deliver timolol.

	Solution 1	Solution 2
Timolol maleate	0.68%	0.68%
Tetronic 1307	22.0%	27.0%
pH adjusted with HCl to	4	4
sufficient water to make	100%	100%
gel-sol transition temperature	30°	26°

The thermally gelling solutions 1 and 2 were compared to the commercially available Timoptic® solution (Timolol maleate 0.68%). The experiment involved measurement of the lacrimal fluid concentration of the drug with time. Even though a biological response is not measured, the effect of the thermally gelling solutions in maintaining higher drug concentrations for extended periods of time provides an indication of the response the drug should have. The solutions can be compared from the first-order decay rates and AUC.

Solution	Half-life	Relative AUC
Solution 1	3.8 min.	2.7
Solution 2	13 min.	3.3
Timoptic[R]	1.1 min.	1

The thermally gelling solutions provide much slower elimination rates of the drug from eye.

EXAMPLE 3

The use of the polymer vehicle to deliver Norfloxacin.

	Solution 1	Solution 2	Solution 3	Solution 4
Norfloxacin	0.1%	0.1%	0.1%	0.1%
Tetronic 1307	22.0%	27.0%	32.0%	—
pH adjusted with HCl to	4	4	4	4
sufficient purified water to make	100%	100%	100%	100%
gel-sol transition temp.	30° C.	26° C.	21° C.	—

The concentration of norfloxacin was measured in the lacrimal fluid with time. The elimination rates of norfloxacin were slower for the thermally gelling solutions 1, 2 and 3 and produced larger AUC.

Solution	Relative AUC
1	2.2
2	1.7
3	1.9
4	1

EXAMPLE 4

	Solution 1	Solution 2
Norfloxacin	0.4%	0.2%
Tetronic 1307	27.0%	0.0%
pH adjusted with HCl to	4	4
sufficient purified water to make	100%	100%

The solutions in Example 4 can be used to demonstrate that a larger dose of drug can be administered in the thermally gelling solution without exceeding the saturation level of the drug. Solutions 1 and 2 in the rabbit eye both give initial concentrations of about 2 mg/ml even though solution 1 has twice the concentration. The slower release from such a thermally gelling solutions would be of value under such conditions.

EXAMPLE 5

Dexamethasone	0.05%
Tetronic 1307	30.0%
Benzalkonium chloride	0.02%
pH adjusted with HCl to	4
sufficient purified water to make	100%
gel-sol transition temperature	21°

EXAMPLE 6

Gentamycin Sulfate	0.1%
Tetronic 1307	25.0%
Benzalkonium chloride	0.01%
Sodium chloride	0.05%
pH adjusted with HCl to	4
sufficient purified water to make	100%
gel-sol transition temperature	26°

EXAMPLE 7

Chloramphenicol	0.5%
Tetronic 1508	20.0%
Sodium acetate	0.3%
Benzalkonium chloride	0.01%
pH adjusted with HCl to	5
sufficient purified water to make	100%
gel-sol transition temperature	27°

If the pharmaceutical compositions of Examples 5–7 were compared with similar compositions but without the polymer, it would be expected that the compositions of Examples 5–7 would result in greater bioavailability and/or sustained concentrations of the drug in the eye.

Following the procedure of Examples 1–6 one can use an appropriate amount of the polymers listed below in place of the Tetronic 1307 or Tetronic 1508 polymer used in Examples 1–6 and 7.

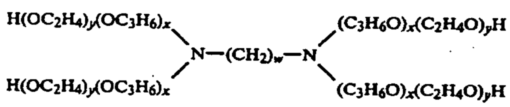
Tetronic 1107
Tetronic 908
Tetronic 707

Following the procedure of Examples 1–7 one can use an appropriate amount of the drugs or medicaments previously enumerated in this application in place of the drug or medicament used in Examples 1–7.

What is claimed is:

1. An aqueous pharmaceutical composition for treating an eye condition requiring pharmacological treatment comprising

a. 10% to 50% by weight of a polymer of the formula



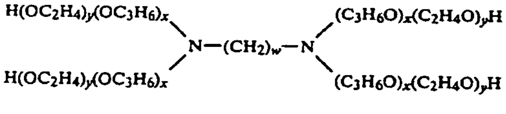
wherein w is an integer from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20 to 60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints,

b. a pharmacologically effective amount of a pharmaceutical or diagnostic agent; and,

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9 and wherein the composition is liquid at about room temperature or below.

2. An aqueous pharmaceutical composition for treating an eye condition requiring pharmacological treatment comprising

a. 10% to 50% by weight of a polymer of the formula



wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20 to 60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints,

b. a pharmacologically effective amount of a drug selected from the group consisting of antibacterial substances, antihistamines and decongestants, anti-inflammatories, miotics and anticholinergics, mydriatics, antiglaucoma drugs, antiparasitics, antiviral effective compounds, carbonic anhydrase inhibitors, anesthetic agents, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, immunosuppressive agents and anti-metabolites or combinations of any of the above; and,

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9 and wherein the composition is liquid at about room temperature or below.

3. The composition of claim 2 wherein the polymer is one where w is 2.

4. The composition of claim 2 wherein the polymer is Tetronic 1307®.

5. The composition of claim 2 wherein the gel-sol transition temperature of the composition is room temperature or below and said composition is liquid at this temperature.

6. The composition of claim 2 wherein the antibacterial substances are selected from the group consisting of beta lactam antibiotics, tetracyclines, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, chloramphenicol, neomycin, gramicidin, bacitracin, cefazolin, cephaloridine, chibrorifamycin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and norfloxacin and the antimicrobial combination of fludalanine/pentizidone.

7. The composition of claim 2 wherein the antihistaminics and decongestants are selected from the group consisting of perilamine, chlorpheniramine, tetrahydrazoline and antizoline.

8. The composition of claim 2 wherein the antiinflammatory drugs are selected from the group consisting of hydrocortisone acetate, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, methyl prednisolone, medrysone, fluorometholone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide.

9. A composition of claim 2 wherein the miotics and anticholinergics are selected from the group consisting of echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, carbachol, methacholine, bethanechol, epinephrine, dipivefrin, neostigmine, echothiopateiodide and demecium bromide.

10. The composition of claim 2 wherein the mydriatics are selected from the group consisting of atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium and eucatropine.

11. The composition of claim 2 wherein the antiglaucoma drugs are selected from the group consisting of timolol, R-timolol, the hydrogen maleate salt of timolol, the combination of timolol and R-timolol with pilocarpine, epinephrine and epinephrine complex or prodrugs and hyperosmotic agents.

12. A composition of claim 2 wherein the antiparasitic or antiprotozoal compound is ivermectin, pyrimethamine, trisulfapyrimidone, clindamycin and corticosteroid preparations.

13. The composition of claim 2 wherein the antiviral effective compounds are selected from the group con-

sisting of acyclovir, interferon, 5-iodo-2'-deoxyuridine, adenosine, arabinoside and trifluorothymidine.

14. The composition of claim 2 wherein the carbonic anhydrase inhibitors are selected from the group consisting of 2-(p-hydroxyphenyl)thio-5-thiophenesulfonimide, 6-hydroxy-2-benzothiazolsulfonamide, 6-pivaloyloxy-2-benzothiazolesulfonamide, acetazolamide, and dichlorphenamide.

15. The composition of claim 2 wherein the antifungal agents are selected from the group consisting of amphoterium B, nystatin, flucytosine, natamycin and miconazole.

16. The composition of claim 2 wherein the anesthetic agent is selected from the group consisting of etidocaine, cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine.

17. The composition of claim 2 wherein the chelating agent is selected from the group consisting of ethylenediamine tetra-acetate and deferoxamine.

18. The composition of claim 2 wherein the immunosuppressive agent and anti-metabolite is selected from the group consisting of methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine.

19. The composition of claim 2 which includes a buffering agent or salt of from 0 to 5% by weight of the composition.

20. The composition of claim 19 wherein the buffering agent or salt is selected from the group consisting of alkali or alkali earth carbonates, chlorides, sulfates, phosphates, bicarbonates, citrates, borates, acetates and succinates.

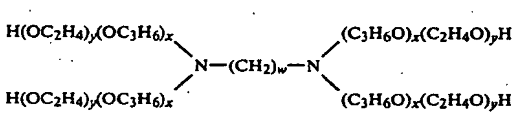
21. The composition of claim 2 which includes from 0.001% to 5% by weight of the composition of a preservative.

22. The composition of claim 21 wherein the preservatives are selected from the group consisting of sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol and phenylethanol.

23. The composition of claim 2 wherein the acid or base is selected from the group consisting of hydrochloric acid or sodium hydroxide.

24. An aqueous pharmaceutical composition for treating an eye condition requiring pharmacological treatment comprising

a. 10% to 50% by weight of a polymer of the formula



wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20-60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints; and,

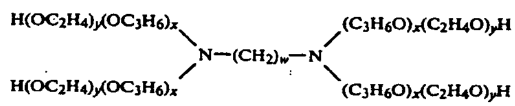
b. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9.

25. A composition of claim 24 which includes a buffering agent or salt of from 0 to 5% by weight of the composition.

26. A composition of claim 24 which includes a preservative of from 0.001% to 5% by weight of the composition.

27. A method of treating an eye condition requiring pharmacological treatment or administration of a diagnostic agent which comprises administering to the eye a liquid drug delivery vehicle comprising:

a. 10% to 50% by weight of a polymer of the formula



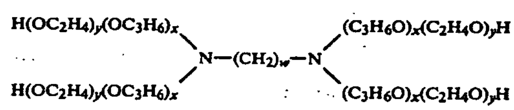
wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20-60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints,

b. a pharmacologically effective amount of a pharmaceutical or diagnostic agent; and,

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9.

28. A method of treating an eye condition requiring pharmacological treatment or administration of a diagnostic agent which comprises administering to the eye a liquid drug delivery vehicle comprising:

a. 10% to 50% by weight of a polymer of the formula



wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20-60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints,

b. a pharmacologically effective amount of a drug selected from the group consisting of antibacterial substances, antihistamines and decongestants, anti-inflammatories, miotics and anticholinergics, mydriatics, antiglaucoma drugs, antiparasitics, antiviral effective compounds, carbonic anhydrase inhibitors, anesthetic agents, opthalmic diagnostic agents, opthalmic agents used as adjuvants in surgery, chelating agents, immunosuppressive agents and antimetabolites or combinations of the above; and

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9.

29. A method of treatment according to claim 28 wherein the polymer is one wherein w=2.

30. A method of treatment according to claim 28 wherein the polymer is Tetronic 1307®.

31. A method of treatment according to claim 28 wherein the gel-sol transistion temperature of the composition is room temperature or below and said composition is liquid at this temperature.

32. A method of treatment according to claim 28 wherein the antibacterial substances are selected from the group consisting of beta-lactam antibiotics, tetracy-

clines, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, chloramphenicol, neomycin, gramicidin, bacitracin, cefazolin, cephaloridine, chibro-rifamycin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone.

33. A method of treatment according to claim **28** wherein the antihistaminics and decongestants are selected from the group consisting of perilamine, chlorpheneramine, tetrahydrazoline and antizoline.

34. A method of treatment according to claim **28** wherein the antiinflammatory drugs are selected from the group consisting of hydrocortisone acetate, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, methyl prednisolone, medrysone, fluorometholone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide.

35. A method of treatment of claim **28** wherein the miotics and anticholinergics are selected from the group consisting of echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, carbachol, methacholine, bethanechol, epinephrine, dipivalylepinephrine, neostigmine, echothiopateiodide and demecium bromide.

36. A method of treatment according to claim **28** wherein the mydriatics are selected from the group consisting of atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium and eucatropine.

37. A method of treatment according to claim **28** wherein the antiglaucoma drugs are selected from the group consisting of timolol, R-timolol, the hydrogen maleate salt of timolol, the combination of timolol and R-timolol with pilocarpine, epinephrine, dipivefrin and epinephrine complex or prodrugs and hyperosmotic agents.

38. A composition of claim **28** wherein the antiparasitic or anti-protozoal compound is ivermectin, pyrimethaxine, trisulfapyrimidon, clindamycin and corticosteroid preparations.

39. A method of treatment according to claim **28** wherein the antiviral effective compounds are selected from the group consisting of acyclovir, interferon, 5-iodo-2'-deoxy uridine, adenosine, arabinoside and trifluorothymidine.

40. A method of treatment according to claim **28** wherein the carbonic anhydrase inhibitors are selected from the group consisting of 2-(p-hydroxyphenyl)thio-5-thiophenesulfonimide, 6-hydroxy-2-benzothiazolesulfonamide, 6-pivaloyloxy-2-benzothiazolesulfonamide, acetazolamide and dichlorphenamide.

41. The method of treatment according to claim **28** wherein the antifungal agents are selected from the group consisting of amphoterium B, nystatin, flucytosine, natamycin and miconazole.

42. The method of treatment according to claim **28** wherein the anesthetic agent is selected from the group consisting of etidocaine, cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine.

43. The method of treatment according to claim **28** wherein the chelating agent is selected from the group consisting of ethylenediamine tetra-acetate and deferoxamine.

44. The method of treatment according to claim **28** wherein the immunosuppressive agent and anti-metabolite is selected from the group consisting of methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine.

45. A method of treatment according to claim **28** wherein the composition includes a buffering agent or salt of from 0% to 5% by weight of the composition.

46. A method of treatment according to claim **45** wherein the buffering agent or salt is selected from the group consisting of alkali or alkali earth carbonates, chlorides, sulfates, phosphates, bicarbonates, citrates, borates, acetates and succinates.

47. A method of treatment according to claim **28** wherein the composition includes from 0.001% to 5% by weight of the composition of a preservative.

48. A method of treatment according to claim **47** wherein the preservatives are selected from the group consisting of sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol and phenylethanol.

49. A method of treatment according to claim **28** wherein the acid or base is selected from the group consisting of hydrochloric acid or sodium hydroxide.

50. A methou of treating a dry eye which comprises administering to the eye a liquid drug delivery device comprising

a. 10% to 50% by weight of a polymer of the formula

$$\begin{array}{ccc} H(OC_2H_4)_y(OC_3H_6)_x & & (C_3H_6O)_x(C_2H_4O)_yH \\ & \diagdown \quad \diagup & \\ & N-(CH_2)_w-N & \\ & \diagup \quad \diagdown & \\ H(OC_2H_4)_y(OC_3H_6)_x & & (C_3H_6O)_x(C_2H_4O)_yH \end{array}$$

wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20–60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints; and,

b. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9.

51. A method of treatment of claim **50** wherein the composition includes a buffering agent or salt of from 0% to 5% by weight of the composition.

52. A method of treatment of claim **50** wherein the composition includes a preservative of from 0.001% to 5% by weight of the composition.

53. The composition of claim **6** wherein the β-lactam antibiotics are selected from the group consisting of cefoxitin, n-formamidoyl thienamycin and other thienamycin derivatives.

54. A method of treatment of claim **32** wherein the β-lactam antibiotics are selected from the group consisting of cefoxitin, n-formamidoyl thienamycin and other thienamycin derivatives.

* * * * *

US005192535A

United States Patent [19]

Davis et al.

[11] **Patent Number: 5,192,535**

[45] **Date of Patent: Mar. 9, 1993**

[54] **OPHTHALMIC SUSPENSIONS**

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[21] Appl. No.: **544,518**

[22] Filed: **Jun. 27, 1990**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 537,005, Jun. 12, 1990, abandoned, which is a continuation of Ser. No. 301,114, Jan. 25, 1989, abandoned, which is a continuation-in-part of Ser. No. 153,762, Feb. 8, 1988, abandoned.

[51] **Int. Cl.**[5] **A61F 2/14**; A61K 9/64; A61K 9/70; A61K 31/765

[52] **U.S. Cl.** **424/78.04**; 424/427; 424/428; 424/443; 424/484; 424/486; 424/487; 514/772.3; 514/772.4; 514/772.6; 514/912; 514/913; 514/914; 514/915; 514/944; 514/953; 514/954

[58] **Field of Search** 424/78, 427, 428, 443, 424/456, 484, 486, 487, 78.04; 514/724, 912, 913, 914, 915, 944, 953, 954, 772.3-772.04, 772.6; 526/317.1, 318, 318.3, 318.5, 319

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Primary Examiner—Thurman K. Page
Assistant Examiner—Carlos Azpuru
Attorney, Agent, or Firm—Freed, Kjeldgaard, Griffin & Inskeep

[57] **ABSTRACT**

Lightly crosslinked polymers, preferably ones prepared by suspension or emulsion polymerizing at least about 90% by weight of a carboxyl-containing monoethylenically unsaturated monomer such as acrylic acid with from about 0.1% to about 5% by weight of a polyfunctional, and preferably difunctional, crosslinking agent such as divinyl glycol (3,4-dihydroxy-1,5-hexadiene), having a particle size of not more than about 50 μm in equivalent spherical diameter, when formulated with an ophthalmic medicament, e.g., fluorometholone, into suspensions in aqueous medium in which the amount of polymer ranges from about 0.1% to about 6.5% by weight, based on the total weight of the aqueous suspension, the pH is from about 3.0 to about 6.5, and the osmotic pressure (osmolality or tonicity) is from about 10 mOsM to about 400 mOsM, provide new topical ophthalmic medicament delivery systems having suitably low viscosities which permit them to be easily administered to the eye in drop form, and hence be comfortably administrable in consistent, accurate dosages. These suspension will rapidly gel in the eye after coming into contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension and thus remain in place for prolonged periods of time to provide sustained release of the ophthalmic medicament.

35 Claims, No Drawings

OPHTHALMIC SUSPENSIONS

REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 07/537,005, now abandoned, filed on June 12, 1990, which was a file wrapper continuation of application Ser. No. 301,114, now abandoned filed Jan. 25, 1989, which was a continuation-in-part of application Ser. No. 153,762, now abandoned filed Feb. 8, 1988. The entire disclosures of those applications are hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to new polymer systems for topical ophthalmic application and to their preparation. More particularly, this invention relates to new topical ophthalmic delivery systems for controlled, sustained release of medicaments after administration in reliable drop form at a suitable initial viscosity which then substantially increases upon contact with the tear fluid.

BACKGROUND OF THE INVENTION

In topical administration of medicaments to the eye, a variety of factors can be important, among them comfort, consistency and accuracy of dosage, type and time of any vision interference, ease of administration, and timing of delivery. Prior ophthalmic delivery vehicles have suffered drawbacks in one or more of those areas.

For example, eyedrops in the form of aqueous solutions or suspensions are rapidly washed away by the eye's tear fluid. Ointments or creams blur the vision, and also have comparatively short residence times in the eye. Gelatin lamellae or other films or sheets, ocular inserts and non-aqueous suspensions and emulsions all can cause immediate pain and continuing discomfort and can also interfere with vision.

Highly viscous aqueous gels formed from carboxy vinyl polymers, such as those disclosed in Schoenwald et al. U.S. Pat. Nos. 4,271,143 and 4,407,792, issued June 2, 1981 and Oct. 4, 1983, respectively, are difficult to administer so as to provide consistent, accurate dosages and may be uncomfortable to administer as well. Indeed, above a viscosity of about 30,000 cps, reliable administration in drop form is at best difficult to achieve and at worst impossible. However, at viscosities low enough for reliable administration in drop form, such low viscositiies impose an undesirable limitation on delivery efficiency because they render the suspension more amenable to dilution by tears Of course, higher viscosity suspensions may be employed in an effort to get the suspensions to remain in the eye for a prolonged time period, but such higher viscosities impair ease of administration of accurate drop dosages.

UK Patent Application No. GB 2007091A (Toko) describes carboxy vinyl polymer based gels over a wider viscosity range, namely 1,000 to 100,000 cps. The relatively low viscosity preparations having viscosities of 1,000 to 10,000 are stated to have good flowability and to be amenable to application by drops directly into the mucous membrane around the eyeball. The preparations having viscosities of from 10,000 to 100,000 cps are stated to be amenable to application to the eyelids like conventional ointments. However, in both higher and lower viscosity situations it is stated that the tears liquify the gel. The use of sodium chloride in the preparation is recommended in Toko for sustained efficiency because sodium chloride is said to delay breakdown of the gel when the compositions are applied to the mucous membrane of the eye. However, the sodium chloride is also said to convert the gel to a liquid with a great reduction in viscosity. Therefore, when sodium chloride is added to the composition, increased polymer amounts are recommended to compensate for such viscosity reduction due to the addition of sodium chloride.

Although delaying breakdown of a gel of a given viscosity by using the Toko teachings might have some benefits, it is that given viscosity which will influence whether reliable administration in drop form is achievable or whether ointment-like administration, together with its dosage problems, will be dictated. Whether the alleged sustained efficiency benefit said in Toko to be associated with a sodium chloride additive could even be accomplished at viscosities suitable for drop administration is far from clear from Toko. Nevertheless, even if such a benefit could be obtained with a Toko formulation at a viscosity for administration by drops, the fact that the starting viscosity is at a level low enough to even permit administration by drops is itself limiting on the so-called sustained efficiency. Indeed, as stated in the Toko document, when the preparations are applied, the tears liquify the gel. The sodium chloride merely is said to delay that breakdown.

It would, therefore, be desirable to provide an ophthalmic delivery system which is administrable at a viscosity suitable for reliable drop dosages, but which substantially increases in viscosity after administration. In that way, the drawbacks of either higher or lower viscosity need not be accepted in order to obtain the benefit of the other.

Robinson, U.S. Pat. No. 4,615,697, issued Oct. 7, 1986, discloses a controlled release treatment based on a bioadhesive which is described as a water-swellable, although water insoluble, fibrous, cross-linked carboxyfunctional polymer with a plurality of repeating units in which about at least 80 percent thereof contain at least one carboxy functionality and a crosslinking agent (0.05 to 1.5 percent) that is substantially free of polyalkenyl polyether. It is, first of all, noteworthy that whereas Robinson seeks to exclude the use of polyalkenyl polyether crosslinkers (as are present in Carbapol 934), Toko finds Carbapol 934 especially useful. Moreover, quite apart from that, Robinson neither discloses nor suggests a suspension that is administrable in drop form at a suitable viscosity and which undergoes rapid gelation upon contact with the tears.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of this invention to provide new topical ophthalmic medicament delivery methods and systems (and methods of their preparation) which overcome or minimize problems of the sort previously noted.

It is also an object of this invention to provide new topical ophthalmic medicament delivery methods and systems that are easily administrable to the eye in drop form.

A further object of this invention is to provide such new topical ophthalmic medicament delivery methods and systems which employ aqueous suspensions of particular lightly crosslinked polymers of acrylic acid or the like containing an ophthalmic medicament.

Yet another object of this invention is to provide new topical ophthalmic medicament delivery systems that are easily administrable in drop form and, after coming

into contact with the eye's tear fluid, rapidly gel in the eye to a substantially greater viscosity than the viscosity of the administered drop.

A still further object of this invention is to provide methods of preparing these new topical ophthalmic medicament delivery systems.

In accordance with a preferred form of the invention intended to accomplish at least some of the foregoing objects, a sustained release topical ophthalmic medicament delivery system comprises an aqueous suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM containing from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a crosslinking agent, such weight percentages of monomers being based on the total weight of monomers polymerized. The suspension has an initial viscosity of from about 1,000 to about 30,000 centipoises and is administrable to the eye in drop form at that initial viscosity. The polymer has average particle size of not more than about 50 μm, preferably not more than about 30 μm, in equivalent spherical diameter. It is lightly cross-linked to a degree such that although the suspension is administrable in drop form, upon contact of the lower pH suspension with the higher pH tear fluid of the eye, the suspension is rapidly gellable to a substantially greater viscosity than the viscosity of the suspension as originally administered in drop form. Accordingly, the resulting more viscous gel can remain in the eye for a prolonged period of time so as to release a medicament contained therein in sustained fashion.

The polymer is preferably prepared from at least about 50% by weight, more preferably at least about 90% by weight, of one or more carboxyl-containing monoethylenically unsaturated monomers. Desirably the polymer is prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional crosslinking agent to a particle size of not more than about 50 μm, preferably not more than about 30 μm, in equivalent spherical diameter. A preferred crosslinking agent is divinyl glycol. It may be desirable to replace up to about 40% by weight of the carboxyl-containing monoethylenically unsaturated monomers by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically and ophthamologically innocuous substituents.

The osmotic pressure is preferably achieved by using a physiologically and ophthalmologically acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspensions. A preferred salt is sodium chloride.

Medicament may be present in desired amount, preferably 0.005% to about 10% by weight, based on the total weight of the suspension. Preferred medicaments include fluorometholone and pilocarpine.

In a preferred method of preparing sustained release topical ophthalmic delivery systems, the foregoing suspensions are prepared and packaged at the desired viscosity of from 1,000 to about 30,000 centipoises, for administration to the eye in drop form. In a preferred delivery method, the foregoing suspensions, containing the medicament, are administered to the eye at the initial viscosity in drop form to cause the administered suspension, upon contact with the higher pH tear fluid of the eye, to rapidly gel in situ to a substantially greater viscosity than the viscosity of the suspension as originally administered in drop form. The more viscous gel remains in the eye for a prolonged period of time so as to release the medicament, entrapped in the more viscous gel formed in the eye, in sustained fashion.

In contrast to other systems, the present invention provides an ophthalmic delivery system that not only has the benefits of administration in drop form, but also does not suffer from breakdown limitations due to administration at a viscosity suitable for drops. Through administration at a viscosity such that the suspension can be reliably administered in drop form, but which actually increases when the suspension is so administered, controlled release of medicament is significantly enhanced.

As mentioned above, viscosities substantially over 30,000 cps are not suitable for drops. When the viscosities are substantially lower than 1,000 cps, the ability to gel upon contact with tears is impeded. The increased gelation upon contact with the tears occurs with a pH change when the suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM contacts the tear fluid. As will be appreciated, tear fluid is at a higher pH of about 7.2 to about 7.4. With the pH increase, carboxylic acid (COOH) undergoes a sodium replacement (to COONa), and the sodium form disassociates, causing the polymer to expand.

This is where relationships of crosslinking and particle size become quite significant. Because the particles are present in a suspension, the degree of crosslinking is necessarily at a level such as to have avoided substantial dissolution of the polymer. On the other hand, since rapid gelation is achieved at the time of the pH change, the degree of crosslinking is necessarily not so great that gelation is precluded. Moreover, if the polymer particle size is too large, induced swelling can tend to take up voids in the volume between large particles that are in contact with one another, rather than the swelling tending to cause gelation.

If the polymer were in a dissolved state, as it would be if there were insufficient crosslinking because of a too low of a ratio of crosslinker to monomer, particle size would be basically irrelevant. In a suspension, particle size can be relevant to comfort. However, it has been found that in the system of the present invention, the small particle size and light crosslinking synergistically yield rapid gelation to a substantially increased viscosity when the pH changes. In fact, above the 50 μm size this advantage of substantially increased viscosity is not realized. Moreover, at the 50 μm size, there is also reasonably good eye comfort.

Although there has been prior disclosure that small particles are desirable to avoid vision impairment (Robinson, supra, col. 10, lines 16–20), that disclosure has not taught particle size limits contemplated for the present invention, especially not for realization of the in situ gelation benefits achievable by such sizes with appropriate light crosslinking in a system where viscosity is at an initial level suitable for drop administration, but which substantially increases upon tear contact.

In the most preferred forms of the invention, the particles are not only subject to the upper size limits described above, but also to a narrow particle size distribution. Such use of a monodispersion of particles, which aids in good particle packing, yields a maximum increased viscosity upon contact of the suspension with the tears and increases eye residence time. At least

about 80%, more preferably at least about 90% and most preferably at least about 95%, of the particles should be within a no more than about 10 μm band of major particle size distribution, and overall (i.e., considering particles both within and outside such band) there should be no more than about 20%, preferably no more than about 10% and most preferably no more than about 5% fines (i.e., particles of a size below 1 μm. It is also preferred that as the average particle size is lowered from the upper limit of 50 μm, more preferably 30 μm, to lower sizes such as 6 μm, that the band of major particle size distribution be also narrowed, for example to 5 μm. Preferred sizes for particles within the band of major particle distribution are less than about 30 μm, more preferably less than about 20 μm, most preferably from about 1 μm to about 5 μm.

The foregoing and other aspects, objects and advantages of the present invention, as well as its nature, scope and utilization, will become more apparent to those skilled in the art from the following detailed description and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The lightly crosslinked polymers of acrylic acid or the like used in practicing this invention are, in general, well known in the art. In a preferred embodiment such polymers are ones prepared from at least about 90% and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxyl-containing monoethylenically unsaturated monomers. Acrylic acid is the preferred carboxyl-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxyl-containing monomers, such as methacrylic acid, ethacrylic acid, β-methylacrylic acid (crotonic acid), cis-α-methylcrotonic acid (angelic acid), trans-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, β-phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), umbellic acid (p-hydroxycoumaric acid), and the like can be used in addition to or instead of acrylic acid.

Such polymers are crosslinked by using a small percentage, i.e., less than about 5%, such as from about 0.5% or from about 0.1% to about 5%, and preferably from about 0.2% to about 1%, based on the total weight of monomers present, of a polyfunctional crosslinking agent. Included among such crosslinking agents are non-polyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide and the like. Also included are polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal $H_2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown U.S. Pat. No. 2,798,053. Diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as insoluble di- and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalxyl acrylate or methacrylate reaction products, and reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the crosslinking agents; see, e.g., Mueller et al. U.S. Pat. Nos. 4,192,827 and 4,136,250.

The lightly crosslinked polymers can of course be made from a carboxyl-containing monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. They can also be polymers in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxyl-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically and ophthalmologically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see Mueller et al. U.S. Pat. No. 4,548,990 for a more extensive listing of such additional monoethylenically unsaturated monomers. Particularly preferred polymers are lightly crosslinked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene.

The lightly crosslinked polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm, and preferably from about 3 to about 20 μm, in equivalent spherical diameter. In general, such polymers will range in molecular weight estimated to be about 250,000 to about 4,000,000, and preferably about 500,000 to about 2,000,000.

Aqueous suspensions containing polymer particles prepared by suspension or emulsion polymerization whose average dry particle size is appreciably larger than about 50 μm in equivalent spherical diameter are less comfortable when administered to the eye than suspensions otherwise identical in composition containing polymer particles whose equivalent spherical diameters are, on the average, below about 50 μm. Moreover, above the average 50 μm size, the advantage of substantially increased viscosity after administration is not realized. It has also been discovered that lightly crosslinked polymers of acrylic acid or the like prepared to a dry particle size appreciably larger than about 50 μm in equivalent spherical diameter and then reduced in size, e.g., by mechanically milling or grinding, to a dry particle size of not more than about 50 μm in equivalent spherical diameter do not work as well as polymers made from aqueous suspensions. While we do not wish to be bound by any theory or mechanism advanced to explain the functioning of this invention, one possible explanation for the difference of such mechanically milled or ground polymer particles as the sole particulate polymer present is that grinding disrupts the spatial geometry or configuration of the larger than 50 μm lightly cross-linked polymer particles, perhaps by removing uncross-linked branches from polymer chains, by producing particles having sharp edges or protrusions, or by producing ordinarily too broad a range of particle sizes to afford satisfactory delivery

system performance. A broad distribution of particle sizes will impair the viscosity-gelation relationship. In any event, such mechanically reduced particles are less easily hydratable in aqueous suspension than particles prepared to the appropriate size by suspension or emulsion polymerization, and also are less able to gel in the eye under the influence of tear fluid to a sufficient extent and are less comfortable once gelled than gels produced in the eye using the aqueous suspensions of this invention. However, up to about, 40% by weight, e.g., from about 0% to over 20% by weight, based on the total weight of lightly crosslinked particles present, of such milled or ground polymer particles can be admixed with solution or emulsion polymerized polymer particles having dry particle diameters of not more than about 50 μm when practicing this invention. Such mixtures will also provide satisfactory viscosity levels in the ophthalmic medicament delivery systems and in the in situ gels formed in the eye coupled with ease and comfort of administration and satisfactory sustained release of the medicament to the eye, particularly when such milled or ground polymer particles, in dry form, average from about 0.01 to about 30 μm, and preferably from about 1 to about 5 μm, in equivalent spherical diameter.

In the most preferred embodiment of the invention, the particles have a narrow particle size distribution within a 10 μm band of major particle size distribution which contains at least 80%, more preferably at least 90%, most preferably at least 95% of the particles. Also, there is no more than 20%, preferably no more than 10%, and most preferably no more than 5% particles of a size below 1 μm. The presence of large amounts of such fines has been found to inhibit the desired gelation upon eye contact. Apart from that, the use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery systems for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

The aqueous suspensions of this invention will contain amounts of lightly crosslinked polymer particles ranging from about 0.1% to about 6.5% by weight, and preferably from about 0.5% to about 4.5% by weight, based on the total weight of the aqueous suspension. They will preferably be prepared using pure, sterile water, preferably deionized or distilled, having no physiologically or ophthalmologically harmful constituents, and will be adjusted to a pH of from about 3.0 to about 6.5, and preferably from about 4.0 to about 6.0, using any physiologically and ophthalmologically acceptable pH adjusting acids, bases or buffers, e.g., acids such as acetic, boric, citric, lactic, phosphoric, hydrochloric, or the like, bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, THAM (trishydroxymethylaminomethane), or the like and salts and buffers such as citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

When formulating the aqueous suspensions of this invention, their osmotic pressure (π) will be adjusted to from about 10 milliosmolar (mOsM) to about 400 mOsM, and preferably from about 100 to about 250 mOsM, using appropriate amounts of physiologically and ophthalmologically acceptable salts. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the aqueous suspension, will give osmolalities within the above-stated ranges. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium bisulfite, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges.

The amounts of lightly crosslinked polymer particles, the pH, and the osmotic pressure chosen from within the above-stated ranges will be correlated with each other and with the degree of crosslinking to give aqueous suspensions having viscosities ranging from about 1,000 to about 30,000 centipoise, and preferably from about 5,000 to about 20,000 centipoise, as measured at room temperature (about 25° C.) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. The correlations of those parameters are also such that the suspensions will gel on contact with tear fluid to give gels having viscosities estimated to range from about 75,000 to about 500,000 centipoise, e.g., from about 200,000 to about 300,000 centipoise, measured as above, depending on pH as observed, for example, from pH-viscosity curves. This effect is noted by observing a more viscous drop on the eye as a set cast. The cast, after setting, can be easily removed.

The viscous gels that result from fluid eyedrops delivered by means of the aqueous suspensions of this invention have residence times in the eye ranging from about 2 to about 12 hours, e.g., from about 3 to about 6 hours. The medicaments contained in these drug delivery systems will be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present. For fluorometholone, for example, release rates in the rabbit eye in excess of four hours, as measured by fluorometholone contained in the aqueous humor, have been observed.

Medicaments—substances used in treating or ameliorating a disease or medical condition—including drugs intended to treat therapeutically the eye itself or the tissues surrounding the eye and drug administered via the ophthalmic route to treat therapeutically a local condition other than one involving the eye, will typically be incorporated in the topical delivery systems of this invention in therapeutically active amounts comparable to amounts administered in other dosage forms, usually in amounts ranging from about 0.005% to about 10% by weight, and preferably from about 0.01% to about 5% by weight, based on the total weight of the formulation. Thus, for example, from about 0.01% to about 1% by weight of the anti-inflammatory steroid fluorometholone can be administered in this manner.

An illustrative but by no means exhaustive listing of such medicaments includes demulcents (for relief of "dry eye"), antibiotics, antivirals, steroids, aminosubstituted steroids, including anti-inflammatory agents, peptides, polypeptides, cardiotonics, antihypertensives, antiallergics, alpha- and betaadrenergic blocking agents, ophthalmic medicaments such as anticataract agents, antiglaucoma agents and ophthalmic antiinflam-

matory agents, ophthalmic lubricating agents, ophthalmic topical or regional anesthetic agents, etc. Specific medicaments that can be used in the present invention include drugs such as pilocarpine, idoxuridine, carbachol, bethanechol, timolol, atenolol, labetolol, metoprolol, nadolol, oxprenolol, pindolol, sotalol, betaxolol, acebutolol, alprenolol, levo-bunolol, p-aminoclonidine, dipivefrin, tetracycline, epinephrine, phenylephrine, eserine, phospholine, aceclidine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, ethacrynic acid, furosemide, amiloride, chlortetracycline, bacitracin, neomycin, polymyxin, polymyxin B, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillins, erythromycin, sulfacetamide, tobramycin, trospectomycin, vancomycin, ciprofloxacin, perfloxacin, olfloxacin, enoxacin, naphazoline hydrochloride, clindamycin, isofluorophate, fluorometholone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, prednisolone acetate, methylprednisolone, fluticasone propionate, betamethasone, triamcinolone, estradiol, ibuprofen, flurbiprofen, naproxen, esters of ibuprofen, flurbiprofen, and naproxen; ketorolac, suprofen, interferons, cromolyn, gancyclovir, aminozolamide, alltrans-retinoic acid (Vitamin A) and the nontoxic, pharmaceutically acceptable salts thereof. Pro-drug counterparts are also within the scope of the present invention. Ophthalmic lubricating agents are materials capable of inducing natural lacrimation or creating artificial lacrimation and include, for example, polyvinylalcohol, cellulose polymers such as hydroxypropyl methyl cellulose, polylactams such as polyvinylpyrrolidone and the like. "Dry eye" formulations that comprise pure water and a lightly crosslinked polymer of the type described hereinabove in an amount within the range also set forth hereinabove, hypotonic in saline and thus having the requisite osmotic pressure but at a pH in the range of about 3 to about 6.5, are also contemplated as being within the scope of this invention. Topical or regional anesthetic agents include ones used during ophthalmic surgery or other ophthalmic procedures, such as lidocaine, cocaine, benoxinate, dibucaine, proparacaine, tetracaine, etidocaine, procaine, hexylcaine, bupivacaine, mepivacaine, prilocaine, chloroprocaine, and the like.

The term "pharmaceutically acceptable salt" refers to those salts of the parent compound that do not significantly or adversely affect the pharmaceutical properties (e.g., toxicity, efficacy, etc.) of the parent compound. Pharmaceutically acceptable salts administrable by means of the aqueous suspensions of this invention include, for example, chloride iodide, bromide, hydrochloride, acetate, nitrate, stearate, pamoate, phosphate and sulfate salts. It is sometimes desirable to use an appropriate salt form of the medicament that increases the water solubility or polar characteristics of the free drug.

The aqueous suspension topical ophthalmic medicament delivery systems of this invention can be formulated in any of several ways. For example the drug, the lightly crosslinked polymer particles, and the osmolality-adjusting salt can be preblended in dry form, added to all or part of the water, and stirred vigorously until apparent polymer dispersion is complete, as evidenced by the absence of visible polymer aggregates. Sufficient pH adjusting agent is then added incrementally to reach the desired pH, and more water to reach 100 percent formula weight can be added at this time, if necessary. Another convenient method involves adding the drug to about 95 percent of the final water volume and stirring for a sufficient time to saturate the solution. Solution saturation can be determined in known manner, e.g., using a spectrophotometer. The lightly crosslinked polymer particles and the osmolality-adjusting salt are first blended in dry form and then added to the drug—saturated suspension and stirred until apparent polymer hydration is complete. Following the incremental addition of sufficient pH adjusting agent to reach the desired pH, the remainder of the water is added, with stirring, to bring the suspension to 100 percent formula weight.

These aqueous suspensions can be packaged in preservative-free, single-dose non-reclosable containers. This permits a single dose of the medicament to be delivered to the eye one drop at a time, with the container then being discarded after use. Such containers eliminate the potential for preservative-related irritation and sensitization of the corneal epithelium, as has been observed to occur particularly from ophthalmic medicaments containing mercurial preservatives. Multiple-dose containers can also be used, if desired, particularly since the relatively low viscosities of the aqueous suspensions of this invention permit constant, accurate dosages to be administered dropwise to the eye as many times each day as necessary. In those suspensions where preservatives are to be included, suitable preservatives are chlorobutanol, Polyquat, benzalkonium chloride, cetyl bromide, and the like.

In order that those skilled in the art can more fully appreciate aspects of this invention, the following examples are set forth. These examples are given solely for purposes of illustration, and should not be considered as expressing limitations unless so set forth in the appended claims.

EXAMPLE I

A pre-blend was prepared by dry-blending together 0.10 weight percent of fluorometholone (11β, 17α-dihydroxy-9α-fluoro-6α-methylpregna-1, 4-diene-3,20-dione), 1 25 weight percent of Carbopol 976 (formerly known as Carbopol EX 55) (a carboxylcontaining polymer prepared by suspension polymerizing acrylic acid and divinyl glycol; The B. F. Goodrich Company) having a particle size of 5 μm, and 0.15 weight percent of sodium chloride. This pre-blend was added to 80 weight percent of deionized water in a vessel and stirred at 20 rpm at about 25° C. for 12 hours. At this point apparent polymer dispersion was complete as evidenced by the absence of visible polymer aggregates.

The resulting aqueous drug-containing suspension was then titrated with lON aqueous sodium hydroxide to pH 4.53; following which additional deionized water was added, with stirring, to bring the final formulation weight to 100 percent. The final aqueous suspension had an osmolality of approximately 50 mOsM and a viscosity of approximately 12,000 centipoise as measured at 25° C. on a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

EXAMPLE II

Fluorometholone, 0.10 weight percent, was added to 80 weight percent of deionized water in a vessel and stirred at 50 rpm at 25° C. for 24 hours to give a saturated aqueous suspension of the drug. Carbopol 976 polymer having a 5 μm particle size, 1.40 weight percent, and 0.25 weight percent of sodium chloride were

blended in dry form and this blend was then added to the drug-saturated suspension, with stirring, at 20 rpm at 25° C. for 12 hours.

The resulting aqueous drug-containing suspension was then titrated with 10N aqueous sodium hydroxide to pH 4.49, following which additional deionized water was stirred into the suspension to bring the final formulation weight to 100 percent. The final aqueous suspension had an osmolality of approximately 90 mOsM and a viscosity of approximately 18,000 centipoise, measured as in Example I.

EXAMPLES III-VIII

These examples relate to the preparation or "dry eye" formulations (Examples III-V) and pilocarpine hydrochloride formulations (Examples VI-VIII) of the present invention. For each example, NaCl and Carbopol 976, in the indicated weights, were dissolved in 100 g of distilled water using a mechanical mixer, after which the resulting formulation was sterilized at 121° C. for 30 to 45 minutes. NaOH was then sterile-filtered to adjust the pH to the indicated range. In the pilocarpine examples, the pilocarpine hydrochloride was added by sterile filtration and the pH was adjusted following the sterilization. Carbopol 976 in all examples had a particle size of 5 μm.

Dry Eye Formulations			
No.	Carbopol 976 (w/w %)	NaCl (w/w %)	pH
III	1.05	0.175	5.6–5.8
IV	1.05	0.050	5.6–5.8
V	0.80	0.600	5.6–5.8

Pilocarpine Hydrochloride Formulations				
No.	Pilocarpine (w/w %)	Carbopol 976 (w/w %)	NaCl (w/w %)	pH
VI	1.0	2.0	0.1–0.9	5.2–5.8
VII	2.0	2.0	0.1–0.9	5.2–5.8
VIII	4.0	2.0	0.1–0.9	5.2–5.8

EXAMPLE IX

Various formulations were compounded to establish that the viscosity of the polymer solution is dependent on particle size. There were used Carbopol 976 and polycarbophil, another polymer within the scope of the present invention. Polycarbophil, as referred to here, is a polyacrylic-acid polymer lightly cross-linked with divinyl glycol, meeting the compendium specifications of the United States Pharmacopeia, and was obtained as an experimental sample from The B. F. Goodrich Company.

A polycarbophil lot was sieved to ranges of greater than 105 μm, less than 105 μm, less than 105 but greater than 75 μm, and less than 75 but greater than 45 μm. A sample was also ground to a size of less than 10 μm.

The general formulation used for all was 1.05 w/w% polymer and 0.2 w/w% NaCl with a pH of 5.2-5.6. The correlation between particle size and viscosity is shown in the following table.

Polymer	Viscosity (cps)*	(Dry) Nominal Particle Size (μm)
Carbopol 976	28,000	5
Polycarbophil	1,080	<105
Polycarbophil	19,800	<10
Polycarbophil	1,800	>105
Polycarbophil	2,800	>75 and <105
Polycarbophil	9,200	>45 and <75
80 parts Carbopol 976/ 20 parts Polycarbophil	19,200	5/<105
90 parts Carbopol 976/ 10 parts Polycarbophil	22,000	5/<105

*Measured at about 25° C. using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

EXAMPLE X

This example is directed to a fluorometholone suspension within the scope of the present invention.

Fluorometholone, 0.10 weight %, was added to 97 weight % of purified water in a vessel and stirred at high speed for 15 minutes to give a finely dispersed aqueous suspension of the drug. Carbopol 976 polymer having a dry particle size of 5 μm, 1.05 weight %, was added to the drug suspension with stirring and mixing was continued for a minimum of 15 minutes. After the 15-minute minimum time had elapsed, 0.20 weight % of sodium chloride was added.

The resulting aqueous drug-containing suspension was sterilized at 121° C. for 45 minutes. The suspension was cooled to about 50° C. and a 10 N sodium hydroxide solution was then sterile filtered into the suspension with stirring to adjust the pH to 5.6–5.8. Additional purified water was sterile filtered into the suspension with stirring to bring the final formulation weight to 100%. The final aqueous suspension had an osmolality of approximately 150 mOsM, a viscosity of approximately 15,700 centipoise, measured at room temperature (about 25° C.) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 RPM, and a pH of about 5.6–5.8.

EXAMPLE XI

Polycarbophil is prepared by suspension polymerizing acrylic acid lightly cross-linked with divinyl glycol. The lot is sieved to sublots such as those in ranges of less than 50 μm, between 40 μm and 50 μm, between 30 μm and 40 μm, less than 30 μm, between 20 μm and 30 μm, between 10 μm and 20 μm, between 5 μm and 15 μm, and less than 5 μm. All of the sublots are sieved to remove the fines, i.e., particles of less than 1 μm. Various monodispersions are then prepared as blends from the sublots. Each of the monodispersions has a major particle size distribution of at least about 80%, more preferably at least about 90%, and most preferably at least about 95%, within a no more than 10 μm band. Of the particles within and outside that band, no more of the total than about 20%, preferably no more than about 10%, and most preferably no more than about 5% are fines. Preferred sizes for particles within the band of major particle distribution are less than about 30 μm, more preferably less than about 20 μm, and most preferably from about 1 μm to about 5 μm.

The monodisperse blends are added to the desired weight percent of deionized water in a vessel and stirred at 20 rpm at about 25° C. for about 12 hours or until apparent polymer dispersion is complete as evidenced by the absence of visible polymer aggregates.

The suspension is then titrated with 10N aqueous sodium hydroxide to a desired pH in the range of from

about 3 to about 6.5. Sodium chloride is added to adjust the desired osmotic pressure to from about 10 mOsM to about 400 mOsM. The suspension contains from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of polycarbophil prepared by suspension polymerization of the acrylic acid and from about 0.1% to about 5% by weight of the divinyl crosslinking agent.

The amounts of lightly crosslinked polymer particles, the pH, the osmotic pressure, and the degree of crosslinking are correlated to yield aqueous suspensions having initial viscosities in the range of from about 1,000 to about 30,000 cps, more preferably from about 5,000 to about 30,000 cps, as measured at room temperature (about 25° C.) using a Brookfield Digital LVT Viscometer. The correlation of these parameters is also such that upon administration in drop form, the suspensions gel on contact with the tear fluid to substantially greater viscosities, preferably in the range of about 75,000 cps to about 500,000 cps, e.g., from about 200,000 cps to about 300,000 cps.

After such administration, the viscous gel remains in the eye for a prolonged period of time and is able to release a medicament contained therein in sustained fashion. In this connection, medicaments such as fluorometholone, pilocarpine or demulcents, in an amount of from about 0.005% to about 10% by weight based on the total weight of the suspension, are added during or after initial formulation.

The above discussion of this invention is directed primarily to preferred embodiments and practices thereof. It will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts described herein can easily be made without departing from the spirit a-d scope of the invention as defined by the following claims.

We claim:

1. A sustained release topical ophthalmic medicament delivery system, comprising:

an aqueous suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM containing from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a crosslinking agent, such weight percentages of monomers being based on the total weight of monomers polymerized,

said suspension having a viscosity of from about 1,000 to about 30,000 centipoises and being administrable to the eye in drop form,

said polymer having average particle size of not more than about 50 μm in equivalent spherical diameter and being lightly cross-linked such that although the suspension is administrable in drop form, upon contact of the lower pH suspension with the higher pH tear fluid of the eye, the suspension is rapidly gellable to a substantially greater viscosity than the viscosity of the suspension as originally administered in drop form,

whereby the resulting more viscous gel can remain in the eye for sustained release of a medicament contained therein.

2. A topical medicament delivery system as in claim 1 in which said polymer is one prepared from at least 50% weight of one or more carboxyl-containing monoethylenically unsaturated monomers.

3. A topical ophthalmic medicament delivery system as in claim 1 containing an ophthalmic medicament.

4. A topical ophthalmic medicament delivery system as in claim 3 in which said polymer has a particle size of not more than about 30 μm.

5. A topical ophthalmic medicament delivery system as in claim 1, claim 2 or claim 3 in which said polymer is a monodispersion of particles.

6. A topical ophthalmic medicament delivery system as in claim 5 wherein at least about 80% of the particles are within a no more than about 10 μm band of major particle size distribution and no more than about 20% of the total particles are fines.

7. The topical ophthalmic medicament delivery system as in claim 5 wherein at least about 90% of the particles are within a no more than about 10 μm band of major particle size distribution, and no more than about 10% of the total particles are fines.

8. The topical ophthalmic medicament delivery system as in claim 5 wherein at least about 95% of the particles are within a no more than about 10 μm band of major particle size distribution, and no more than about 5% of the total particles are fines.

9. The topical ophthalmic medicament delivery system as in claim 6 wherein the band of major particle distribution is from about 1 to about 5 μm.

10. The topical ophthalmic medicament delivery system as in claim 1 wherein the polymer is one in which up to about 40% by weight of said carboxyl-containing monoethylenically unsaturated monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers.

11. A topical ophthalmic medicament delivery system as in claim 4 in which said polymer is one prepared from at least about 90% by weight of one or more carboxyl-containing monoethylenically un-saturated monomers.

12. A topical ophthalmic medicament delivery system as in claim 3 in which said polymer is one prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional crosslinking agent to a particle size of not more than about 50 μm in equivalent spherical diameter.

13. A topical ophthalmic medicament delivery system as in claim 12 in which said crosslinking agent is divinyl glycol.

14. A topical ophthalmic medicament delivery system as in claim 13 in which said osmotic pressure is achieved using a physiologically and ophthalmologically acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspension.

15. A topical ophthalmic medicament delivery system as in claim 14 in which said salt is sodium chloride.

16. A topical ophthalmic medicament delivery system as in claim 15 in which said medicament is present in an amount of from about 0.005% to about 10% by weight, based on the total weight of the suspension.

17. A topical ophthalmic medicament delivery system as in claim 16 in which said medicament is fluorometholone.

18. A topical ophthalmic medicament delivery system as in claim 16 in which said medicament is pilocarpine.

19. A method of delivering an ophthalmic medicament to the eye which comprises:

preparing an aqueous suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM containing an ophthalmic medicament and from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and from less than about 5% by weight of a cross-linking agent, such weight percentages of monomers being based on the total weight of monomers polymerized,

said suspension having a viscosity of from about 1,000 to about 30,000 centipoises, and said polymer having an average particle size of not more than about 50 μm in equivalent spherical diameter and being lightly crosslinked,

administering said suspension to the eye in drop form to cause the suspension, upon contact with the higher pH tear fluid of the eye, to rapidly gel to a substantially greater viscosity than the viscosity of the suspension as originally administered in drop form,

whereby the resulting more viscous gel remains in the eye for sustained release of the medicament contained therein.

20. A method of claim **19** in which said polymer is one prepared from at least 50% weight of one or more carboxyl-containing monoethylenically unsaturated monomers.

21. A method as in claim **19** or claim **20** in which said polymer has a particle size of not more than about 30 μm.

22. A method as in claim **19** or claim **20** in which said polymer is one in which up to about 40% by weight of said carboxyl-containing monoethylenically unsaturated monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically and ophthalmologically innocuous substituents.

23. A method as in claim **19** in which said polymer is one prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional crosslinking agent to a particle size of not more than about 50 μm in equivalent spherical diameter.

24. A method as in claim **23** in which said cross-linking agent is divinyl glycol.

25. A method as in claim **24** in which said osmotic pressure is achieved using a physiologically and ophthalmologically acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspension.

26. A method as in claim **25** in which said salt is sodium chloride.

27. A method as in claim **26** in which said medicament is present in an amount of from about 0.005% to about 10% by weight, based on the total weight of the suspension.

28. A method as in claim **27** in which said medicament is fluorometholone.

29. A method as in claim **28** in which said medicament is pilocarpine.

30. A method as in claim **19**, claim **20** or claim **21** in which said polymer is a monodispersion of particles.

31. A method as in claim **30** wherein at least about 80% of the particles are within a no more than about 10 μm band of major particle size distribution and no more than about 20% of the total particles are fines.

32. A method as in claim **30** wherein at least about 90% of the particles are within the 10 μm band of major particle size distribution, and no more than about 10% of the total particles are fines.

33. A method as in claim **30** wherein at least about 95% of the particles are within a no more than about 5 μm band of major particle size distribution and no more than about 20% of the total particles are fines.

34. A method as in claim **31** wherein the band of major particle distribution is from about 1 to about 5 μm.

35. A method of preparing a sustained release topical ophthalmic delivery systems, comprising: preparing an aqueous suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM and containing from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a crosslinking agent, such weight percentages of monomers being based on the total weight of monomers polymerized, and

packaging the suspension, at a viscosity of from 1,000 to about 30,000 centipoises, for administration to the eye in drop form,

said polymer having average particle size of not more than about 50 μm in equivalent spherical diameter and being lightly cross-linked such that although the suspension is administrable in drop form, upon contact of the lower pH suspension with the higher pH tear fluid of the eye, the suspension is rapidly gellable to a substantially greater viscosity than the viscosity of the suspension as originally administered in drop form.

* * * * *

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United States Patent [19]

Viegas et al.

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[45] Date of Patent: Dec. 24, 1996

[54] MEDICAL USES OF IN SITU FORMED GELS

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[57] **ABSTRACT**

Balanced pH, hyperosmotic, hypoosmotic, or isoosmotic gels are ideal vehicles for drug delivery. They are especially suited for topical body cavity or injection application of drugs or diagnostic agents; for drug or diagnostic agent delivery to the eye of a mammal; as protective corneal shields; or as ablatable corneal masks useful in laser reprofiling of the cornea. The compositions without the addition of a drug or diagnostic agent are useful as medical devices, for instance, in separating surgically or otherwise injured tissue as a means of preventing adhesions.

11 Claims, No Drawings

MEDICAL USES OF IN SITU FORMED GELS

This is a divisional of copending application(s) Ser. No. 07/785,305 filed on Sep.30 1991, now U.S. Pat. No. 5,318, 780.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to drug delivery systems, the prevention of post-surgical adhesions, ophthalmic corneal protective devices, and a surgical device used in the correction, for instance, of corneal ulcers, irregularities, scarring, astigmatism, myopia, and hyperopia.

2. Description of the Prior Art

Over the years, methods have been developed to achieve the efficient delivery of a therapeutic drug to a mammalian body part requiring pharmaceutical treatment. Use of an aqueous liquid which can be applied at room temperature as a liquid but which forms a semisolid gel when warmed to body temperature has been utilized as a vehicle for drug delivery since such a system combines ease of application with greater retention at the site requiring treatment than would be the case if the aqueous composition were not converted to a gel as it is warmed to mammalian body temperature. In U.S. Pat. No. 4,188,373, PLURONIC® polyols are used in aqueous compositions to provide thermally gelling aqueous systems. Adjusting the concentration of the polymer provides the desired sol-gel transition temperature, that is, the lower the concentration of polymer, the higher the sol-Gel transition temperature, after crossing a critical concentration minimum, below which a gel will not form.

In U.S. Pat. Nos. 4,474,751; '752; '753; and 4,478,822 drug delivery systems are described which utilize thermosetting gels; the unique feature of these systems is that both the gel transition temperature and/or the rigidity of the gel can be modified by adjustment of the pH and/or the ionic strength, as well as by the concentration of the polymer.

Other patents disclosing pharmaceutical compositions which rely upon an aqueous gel composition as a vehicle for the application of the drug are U.S. Pat. Nos. 4,883,660; 4,767,619; 4,511,563; and 4,861,760. Thermosetting gel systems are also disclosed for application to injured mammalian tissues of the thoracic or peritoneal cavities in U.S. Pat. No. 4,911,926.

Ionic polysaccnarides have been used in the application of drugs by controlled release. Such ionic polysaccharides as chitosan or sodium alginate are disclosed as useful in providing spherical agglomerates of water-insoluble drugs in the *Journal of Pharmaceutical Sciences* volume 78, number 11, November 1989, Bodmeier et al. Alginates have also been used as a depot substance in active immunization, as disclosed in the *Journal of Pathology and Bacteriology* volume 77, (1959), C. R. Amies. Calcium alginate gel formulations have also found use as a matrix material for the controlled release of herbicides, as disclosed in the *Journal of controlled Release,* 3 (1986) pages 229–233, Pfister et al.

In U.S. Pat. No. 3,640,741, a molded plastic mass composed of the reaction product of a hydrophilic colloid and a cross-linking agent such as a liquid polyol, also containing an organic liquid medium such as glycerin, is disclosed as useful in the controlled release of medication or other additives. The hydrophilic colloid can be carboxymetnyl cellulose gum or a natural alginate gum which is cross-

linked with a polyol. The cross-linking reaction is accelerated in the presence of aluminum and calcium salts.

In U.S. Pat. No. 4,895,724, compositions are disclosed for the controlled release of pharmacological macromolecular compounds contained in a matrix of chitosan. Chitosan can be cross-linked utilizing aldehydes, epichlorohydrin, benzoquinone, etc.

In U.S. Pat. No. 4,795,642, there are disclosed gelatin-encapsulated, controlled-release compositions for release of pharmaceutical compositions, wherein the gelatin encloses a sol id matrix formed by the cation-assisted gellation of a liquid filling composition incorporating a vegetable gum together with a pharmaceutically-active compound. The vegetable gums are disclosed as polysaccharide gums such as alginates which can be gelled utilizing a cationic gelling agent such as an alkaline earth metal cation.

While the prior art is silent with respect to aqueous drug delivery vehicles and isotonicity thereof, osmotic drug delivery systems are disclosed in U.S. Pat. No. 4,439,196 which utilize a multi-chamber compartment for holding osmotic agents, adjuvants, enzymes, drugs, pro-drugs, pesticides, and the like. These materials are enclosed by semipermeable membranes so as to allow the fluids within the chambers to diffuse into the environment into which the osmotic drug delivery system is in contact. The drug delivery device can be sized for oral ingestion, implantation, rectal, vaginal, or occular insertion for delivery of a drug or other beneficial substance. Since this drug delivery device relies on the permeability of the semipermeable membranes to control the rate of delivery of the drug, the drugs or other pharmaceutical preparations, by definition, are not isotonic with mammalian blood.

Corneal protective devices are needed in cases in which corneal injury occurs and the immobilization of the eye using an eye patch is not resorted to. Molded collagen shields have been developed for this use. These are often not satisfactory because they lack sufficient flexibility to adequately conform to the individual corneal curvature. Wetting a collagen shield will increase conformance of the shield to the cornea but fragmentation can occur upon exceeding the flexibility of the collagen shield. The clinical uses of collagen shields are disclosed by Poland et al. in *Journal of Cataract Refractive Surgery,* Volume 14, September 1988, pages 489–491. The author describes the use of collagen shields immersed in tobramycin solution in order to rehydrate the collagen prior to use. These are described as useful following cataract extraction or in patients having nonsurgical epithelial healing problems. More rapid healing of epithelial defects after surgery resulted from the use of the collagen shield. Collagen shields have also been utilized as agents for the delivery of drugs to the cornea as disclosed in Reidy et al Cornea, in press, 1989 the Raven Press, Ltd., New York and Shofner et al, *Opthalmology clinics of North America,* Vol. 2, No. 1, March 1989, pages 15–23.

Refractive surgery has been promoted in the United States and Russia over the past few years but its acceptance has been limited because of the poor predictability of the final optical results which include a resulting glare from incisions that encroach upon the optical zone. Techniques that rely upon the surgical production of corneal incisions have yielded inconsistent results because these surgical incisions in the cornea have been found to vary considerably in depth and length.

Laser keratectomy has been shown to be capable of yielding a more accurately controlled depth of corneal excision since each individual laser pulse excises a specific

amount (0.2 to 10.0 μm) of corneal tissue. Accordingly, the depth of excised tissue is in theory uniform and predictable, provided that the energy distribution is homogeneous across the laser beam. Since the primary locus of astigmatism is in the cornea, surgical intervention for astigmatism is more important than for the correction of other refractive errors, especially since spectacle or contact lens correction is of limited value in compensating for large astigmatic errors.

The excimer laser was introduced to ophthalmology in 1983 (Trokel, S., et al., "Excimer surgery of the cornea," *Am. J. Ophtalmol.* 96:710–715, 1983). The depth of incision with short intense pulses permitted great precision to be achieved in tests on freshly enucleated cow eyes. The photochemical laser-tissue interaction is not thermal, permitting direct breaks of organic molecular bonds without involving optical breakdown in adjacent tissue. Early experimental results in rabbits revealed problems of 1) corneal stromal swelling, probably in response to disturbed water relationships due to compromise of the epithelial barrier and severing of the lamellae and (2) rearrangement of endothelial cells resulting from loss of contact inhibition (Marshall, J., et al., "An ultrastructural study of corneal incisions induced by an excimer laser at 193 nm", *Ophthalmology* 92:749–758, 1985) Experiments with freshly enucleated human eyes indicated that flattening obtained by excimer laser ablation correlated with results of clinical scalpel radial keratotomy, but evaluation of the effects on wound healing and possible damage to adjacent structures was not addressed (Cotliar, A.M., et al., "Excimer laser radial keratotomy," *Ophthalmology* 92:206–208, 1985). It was, however, suggested that this laser may become very useful in applications including penetrating and lamellar keratoplasty, keratomileusis, and epikeratophakia. Control of the area and depth of pulses using photolithographed masks resulted in ability to produce narrow cuts (20 um) and at depths depending on pulse number (Puliafito, Cali., et al., "Excimer laser ablation of the cornea and lens", *Ophthalmology* 92:741–748, 1985). These controlled ablations had only very narrow bands of destruction at the adjacent edges. These studies led to the quantitation of laser ablation (Krue-Gar, R. R. and S. L. Trokel, "Quantitation of corneal ablation by ultraviolet laser light", *Arch Ophthalmol.* 103: 1741–1742, 1985). Excimer far UV radiation can be controlled to produce minimal adjacent tissue damage providing the angle and depth can be precisely controlled. The remaining problem of effects on healing could then be addressed.

Wound healing was assessed in rabbits following excimer laser surface ablation (Hanna, K. D. , et al., "Corneal stromal wound healing in rabbits after 193 nm excimer laser surface ablation", *Arch. Ophthalmol.* 107: 895–901, 1989). Healing appeared to be excellent except when over 85% to 90% of the corneal thickness had been cut. Endothelial cell disruption, junction separation and individual cell dropout occurred with corneal haze development with the deeper cuts. A delivery system designed to deliver predictable depths of cut is, therefore, essential. Similar findings were reported in studies on human blind eyes (Taylor, D. M., et al., "Human excimer laser lamellar Keratectomy" *Ophthalmology* 96: 654–664, 1989). Attention was directed to the challenges of improved procedures and equipment, the problems of individual variation, and the control of biologic responses to trauma before excimer laser lamellar keratectomy could become a clinically useful means of correcting refractive errors. In living monkey eyes, it was concluded that mild, typical wound healing occurred after excimer laser Keratomileusis (Fantes, F. E., et al., "Wound healing after excimer laser keratomileusis [photorefractive keratectomy] in monkeys", *Arch Ophthalmol.* 108: 665–675, 1990). All corneas were epithelialized by 7 days. By 6 weeks, mild to moderate haze was apparent with clearing by 6 to 9 months. The epithelium was thickened at 21 days after ablation, but returned to normal by 3 months. Subepithelial fibroblasts were three times the density of normal keratocytes, but returned to nearly normal numbers by 9 months. One conclusion reached was that control of the contour and uniformity of the ablated surface is important for structural and biological responses of the cornea.

Review of the literature clearly reveals that far UV vaporization (ablation with an excimer laser at 193 nm, for example) is a feasible means to sculpture or reprofile the cornea to correct nearsightedness, farsightedness, astigmatism, corneal scars, corneal densities, etc. The healing appears to parallel or to be equal to healing after scalpel intervention, providing the proper guidelines for pulsing and duration are followed. There remains a need to control the contour and uniformity of the ablated surface. Such control will reduce the adverse structural and biological response of the cornea and insure that a desired corrective change results.

The use of a mask, of nearly identical optical density to the cornea, which can be preformed on the corneal surface so as to provide a smooth surface of exact contour and accurate dimensions would correct many of the problems that have prevented the precise control of the laser beam during keratotomy. This mask would be required to withstand exposure to moist gases direct tangentally to the corneal surface throughout the duration of exposure to the laser to remove ablated debris. The modulation of the beam energy distribution of the laser in a controlled fashion should also be provided by such a corneal mask. The use of a smooth ablatable mask having a known contour and having the density of the cornea would aid in insuring accurate direction and depth of a tangental cut utilizing a laser beam. The ablatable mask of the invention provides such advantages.

Ionic polysaccharides have been used in the application of drugs by controlled release. Such ionic polysaccharides as chitosan or sodium alginate are disclosed as useful in providing spherical agglomerates of water-insoluble drugs in the *Journal of Pharmaceutical Sciences*, volume 78, number 11, November 1989, Bodmeier et al. Alginates have also been used as a depot substance in active immunization, as disclosed in the *Journal of Pathology and Bacteriology*, volume 77, (1959), C. R. Amies. Calcium alginate gel formulations have also found use as a matrix material for the controlled release of herbicides, as disclosed in the *Journal of Controlled Release*, 3 (1986) pages 229–233, Pfister et al. Alginates have also been used to form hydrogel foam wound dressings, as disclosed in U.S. Pat. No. 4,948,575.

SUMMARY OF THE INVENTION

Compositions and a process for drug or diagnostic agent delivery by topical, injection, or body cavity delivery are disclosed. The pharmaceutical compositions in one embodiment of the invention contain pharmacologically active medicaments which are useful in providing treatments to ophthalmic areas of the mammalian body requiring the controlled release application of a medicament or requiring the administration of a diagnostic agent. In addition, the compositions of the invention are useful, with or without the inclusion of a medicament, as injectable compositions for depot drug delivery, as a protective corneal shield, as a

second skin for application to wounds, as an ablatable corneal mask in a laser keratectomy process or, as medical devices, for instance, in the separation of organs, injured in surgical procedures or otherwise, in order to prevent the formation of undesirable adhesions as part of the healing process.

The compositions of the invention provide a physiologically acceptable vehicle having a buffered pH and hypoosmotic, hyperosmotic, or isoosmotic characteristics. The pH and osmotic pressure is, preferably, made similar to bodily fluids, such as lacrimal tears. The pH and osmotic pressure of lacrimal tears is about pH 7.4 and 290 mOsm/kg. In addition, the pharmaceutical compositions are, optionally, sterilized so as to insure that the pharmaceutical compositions of the invention do not provide a source of infection.

Polyphase systems are also useful and may contain non-aqueous solutes, non-aqueous solvents, and other non-aqueous additives. Homogeneous, polyphase systems can contain such additives as water insoluble high molecular weight fatty acids and alcohols, fixed oils, volatile oils and waxes, mono-, di-, and triglycerides, and synthetic, water insoluble polymers without altering the functionality of the system.

The compositions of the invention in a preferred embodiment comprise aqueous mixtures of a film forming, water soluble polymer and an ionic polysaccharide, optionally containing a latent counter-ion to gel the polysaccharide upon release of the counter-ion. Alternatively, the compositions of the invention can comprise a two part aqueous system, one of which contains the ionic polysaccharide and film forming polymer and the other part containing an aqueous solution of a counter-ion.

The counter-ion can be provided in latent form by microencapsulation in a heat sensitive medium, for instance, the walls of the microcapsule can be made of mono-, di-, or tri-glycerides or other natural or synthetic heat sensitive polymer medium. Alternatively, ion exchange resins can be incorporated in the compositions of the invention so as to release the desired counter-ion upon contact with an environment opposite in pH to the pH of the ion exchange resin. The aqueous mixture can be delivered to the ophthalmic area of the mammalian body requiring treatment as a low viscosity liquid at ambient temperatures. Activation of the latent form of the counter-ion gels the aqueous mixture in situ. The two part system can be separately applied to gel the mixture in situ. Because the compositions of the invention are low viscosity liquids at ambient temperatures, they easily pass to various ophthalmic areas insuring maximum contact between exposed tissue and the compositions of the invention. The gel compositions of the invention can be either peeled away or allowed to be absorbed over time. The gels are gradually weakened upon exposure to mammalian body pH conditions.

The useful film forming polymers are, preferably, water soluble polymers such as those which have been used in ophthalmic applications. The hydroxyalkyl cellulosics and methyl celluloses, sodium hyaluronate, and polyvinyl alcohol are representative polymers which have been found useful in ophthalmic applications.

The useful ionic polysaccharides are natural polymers such as chitosan, gellan gum or alginates. Aqueous solutions of alginate ionic polysaccharides form gels upon contact with aqueous solutions of counter-ions such as calcium, strontium, aluminum, etc. Aqueous solutions of chitosan form gels upon contact with a metal tripolyphosphate counter-ion. The discovery forming the bas is of this application is that when ionic polysaccharides are present in aqueous solutions in admixture with film forming polymers and a counter-ion, that such mixtures form useful gels. The osmolality of which can be calculated by assuming that the film forming polymer, if water soluble, does not contribute to the osmolality in the gel state.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that aqueous pharmaceutical vehicles containing a film forming polymer and an ionic polysaccharide can be gelled and rendered resistant to shear thinning by contacting the mixture with a counter-ion. The gel compositions can be made isotonic or iso-osmotic and adjusted to the pH of mammalian body fluids, such as lacrimal tears. The pH and osmotic pressure of such bodily fluids are 7.4 and 290 mOsm/kg, respectively. It is advantageous to deliver a pharmacologically active medicament to an area of the mammalian body requiring pharmacological treatment under desired pH and osmotic pressure conditions which, for instance, match those of bodily fluids. Optionally, the pharmaceutical compositions of the invention can be provided in a sterile condition.

A complete listing of useful water soluble, film forming polymers is not possible. Representative useful polymers are the water soluble alkyl celluloses, i.e., methyl and ethyl cellulose; the hydroxyalkyl celluloses, i.e., hydroxypropylmethyl cellulose and hydroxyethyl cellulose; hyaluronic acid and water soluble salts thereof, i.e., sodium hyaluronate; chondroitin sulfate and water soluble salts thereof, i.e., sodium chondroitin sulfate; polymers of acrylamide, acrylic acid, and polycyanoacrylates; polymers of methyl methacrylate and 2-hydroxyethyl methacrylate; polydextrose, cyclodextrin; polydextrin; maltodextrin, dextran; polydextrose; gelatin, collagen, natural gums, i.e., xanthan, locust bean, acacia, tragacanth, carrageenan, and agar; derivatives of polygalacturonic acid such as pectin; polyvinyl alcohol; polyvinyl pyrrolidone; polyethylene glycol; and polyethylene oxide.

More complete descriptions of some of the preferred water soluble, film forming polymers are as follows. Cyclodextrin also known as cycloamylose is a cyclic oligosaccharide. Cyclodextrins are produced by the enzyme conversion of prehydrolized starch to a mixture of alpha, beta, and gamma cyclodextrins and some linear dextrins. The cyclodextrins are composed of glucose units linked together by alpha (1–4) glycosidic bonds.

Sodium hyaluronate also known as hyaluronic acid is composed of repeating units of sodium glucuronate and N-acetylglucosamine. Sodium hyaluronate was orginally extracted from the comb of the rooster. Hyaluronic acid is a common biological agent present in a number of sources including the human umbilical cord. Sodium hyaluronate can also be manufactured by fermentation of a strain of streptococcus zooepidemicus.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of

which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Further details of the composition and derivation of other useful water soluble, film forming polymers can be found in the *HANDBOOK OF PHARMACEUTICAL EXCIPIENTS*, published by the American Pharmaceutical Association Washington, D.C. copyright 1986, incorporated herein by reference.

The gel forming ionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merck & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or tri-ethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 3.0% by weight and, preferably, about 0.5% to about 1.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

In general, the drug delivery composition of the invention will contain about 0.01% to about 60% by weight of medicament or pharmaceutical, about 1% to about 50% by weight of the water soluble, film forming polymer, together with the above amounts of ionic polysaccharide and the balance water. In special situations, these amounts of gel forming ionic polysaccharide and water soluble, film forming polymer may be varied to increase or decrease the gel properties.

Useful counter-ions for gelling the gellan gum or alginate ionic polysaccharides in combination with the film forming, water soluble polymer compositions of the invention are cationic gelling agents, preferably, comprising a divalent or trivalent cation. Useful divalent cations include the alkaline earth metals, preferably, selected from the group consisting of calcium and strontium. Useful trivalent cations include aluminum. The most preferred counter-ions for gelling gellan gum or alginate ionic polysaccharides are contained in ionic compounds selected from pharmaceutically-acceptable gluconates, fluorides, citrates, phosphates, tartrates, sulfates, acetates, borates, chlorides, and the like having alkaline earth metal cations such as calcium and strontium. Especially preferred counter-ion containing inorganic salts for use as ionic polysaccharide gelling agents include such inorganic salts as the chloride salts, such as strontium chloride, calcium chloride, and mixtures thereof. Generally, a molar ratio of counter-ion to gellan, chitosan or alginate of about 1:1 to about 10:1, preferably, about 2:1 to about 5:1, and, most preferably, about 3:1 to about 5:1 is used.

While the counter-ion, such as calcium or other counter-ions may be obtained by contact of the compositions of the

invention with bodily fluids, it is preferred that a counter-ion in latent form be used in combination with the gellan gum or alginate ionic polysaccharide and film forming, water soluble polymer compositions of the invention. Alternatively, a counter-ion can be combined with the ionic polysaccharide and water soluble, film forming polymer compositions of the invention utilizing a two part system in which the counter-ion is topically or otherwise applied to the compositions of the invention subsequent to their topical or other application.

Incorporation of the counter-ion in a latent form together with the ionic polysaccharide and film forming, water soluble polymer compositions of the invention may be accomplished by either encapsulating an aqueous solution of one of the counter-ion gelling agents, previously described above or by the incorporation of the counter-ion gelling agent into a matrix which provides for the controlled, slow-release of the gelling agent. For instance, the gelatin-encapsulated controlled release compositions disclosed in U.S. Pat. No. 4,795,642, incorporated herein by reference, disclose the preparation of a gelatin shell encapsulating a controlled release formulation in which the gelatin composition includes calcium chloride as the gelling agent. Alternatively, the counter-ion can be incorporated as an aqueous solution of a cationic gelling agent encapsulated in a vesical composed, for instance, of alpha-tocopherol, as disclosed in U.S. Pat. No. 4,861,580, incorporated herein by reference.

Generally, aqueous compositions comprising chitosan can be gelled with multivalent anion gelling agents, preferably, comprising a metal polyphosphate, such as an alkali metal or ammonium polyphosphates, pyrophosphates, or metaphosphates. Representative metaphosphate, pyrophosphate, and polyphosphate gelling agents include sodium and potassium, polyphosphates, sodium and potassium pyrophosphates, sodium and potassium metaphosphates, and sodium and ammonium (mono-, di-, tri-) phosphates.

With specific reference to the use of the compositions of the invention as ophthalmic drug delivery compositions, laser ablatable shields, or corneal protective compositions, it is noted that, generally, for the avoidance of adverse physiological effects to the eye, it is desirable that the pH and osmolality of the pharmaceutical vehicle be matched to the pH and osmolality of the eye. In addition, it is noted that a large percentage of drugs administered to the eye are lost as a result of lacrimal drainage. This applies especially in situations in which a liquid composition containing a pharmacologically active medicament is applied to the cornea of the eye. Accordingly, in such cases, only a small fraction of the pharmaceutical composition administered to the eye remains in contact with the cornea for a few minutes and an even smaller fraction penetrates into the cornea. To overcome these disadvantages, it is known to use viscous solutions, gels, ointments, or solid eye implants containing pharmacologically active medicaments. While progress has been made in the delivery of drugs by the use of solid implants, many patients find it difficult to tolerate the introduction of the implants into the conjunctival areas.

To solve this problem, drug delivery vehicles which are liquid at room temperature and assume a semi-solid form at human body temperature have been proposed, such as those described in U.S. Pat. No. 4,188,373, which disclose the use of PLURONIC® polyols. In U.S. Pat. No. 4,861,760 and U.S. Pat. No. 4,474,751, ophthalmic drug delivery systems are disclosed which show liquid-gel phase transitions. In the '751 Patent, polymers are disclosed which are tetra substituted derivatives of ethylenediamine, propylenediamine, butylenediamine, pentylenediamine, or hexylenediamine.

These are described as block copolymers of poly(oxypropylene) and poly(oxyethylene) of various chain lengths. These polymers were utilized as aqueous drug delivery vehicles contain from 10% to 50% by weight of polymer based on the weight of the total drug delivery vehicle. In the '760 Patent, the liquid-gel phase transition compositions for ophthalmological use contain polymers which form gels at concentrations 10–100 fold lower than those used in systems such as the '751 Patent, involving thermogelation. Accordingly, the drug delivery vehicles of the '760 Patent are said to be very well tolerated by the eye. The polymers utilized in the drug delivery vehicles of the '760 Patent are described as polysaccharides obtained by fermentation of a microorganism.

The drug delivery vehicles and corneal protective shield compositions of the invention are an improvement over those compositions used in prior art methods of ophthalmological drug delivery in that the compositions can be not only optimized for physiological tolerance in the eye by formulating the vehicles useful as drug delivery compositions so as to have isoosmotic, hyperosmotic, and hypoosmotic characteristics in the gel state but are made more useful because of increased resistance to shear thinning, as the result of higher gel strength. These advantages are obtained by the incorporation of an ionic polysaccharide in admixture with a film forming, water soluble polymer. By matching the osmolality of the drug delivery compositions of the invention, for instance, to those of the lacrimal fluid of the eye, it is possible to eliminate burning or other discomfort upon application of the drug delivery vehicles of the invention to the eye. The gel compositions formed upon contact with a counter ion for the ionic polysaccharide allow retention of the gel at the desired locus for longer intervals thus increasing the efficiency of action of the delivered drug. Drugs or diagnostic agents which can be administered by means of the drug delivery vehicles according to the invention are, for example:

- Antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin and sulfonamides;
- aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin;
- nalidixic acid and its analogs such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogs thereof;
- antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogs thereof; mast-cell inhibitors of histamine release, such as cromolyn;
- anti-inflaminatories such as cortisone, hydocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac, its salts and its corresponding sulfides, and analogs thereof;
- miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivaloylepinephrine. neostigmine, echothiopate iodide, demecarium bromide, carbamoyl choline chloride, methacholine, bethanechol, and analogs thereof;
- mydriatics such as atrophine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine, and analogs thereof;

Other drugs can be used in the treatment of conditions and lesions of the eyes such as:

- antiglaucoma drugs, for example, timolol, and especially its maleic salt and R-timolol and a combination of timolol or R-timolol with pilocarpine, as well as many other adrenergic agonists and/or antagonists: epinephrine and an epinephrine complex, or prodrugs such as bitartrate, borate, hydrochloride and dipivefrine derivatives; carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)-thio thiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide, and 6-pivaloyloxy-2-benzothiazolesulfonamide;
- antiparasitic compounds and/or anti-protozoal compounds such as ivermectin, pyrimethamine, trisulfapidimidine, clindamycin and corticosteroid preparations;
- compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, interferon, and interferon-inducing agents such as poly I:C;
- antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole;
- anesthetic agents such as etidocaine cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine;
- ophthalmic diagnostic agents, such as:
  - (a) those used to examine the retina such as sodium fluorescein;
  - (b) those used to examine the conjunctiva, cornea and lacrimal apparatus, such as fluorescein and rose bengal; and
  - (c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine;
  - ophthalmic agents used as adjuncts in surgery, such as alpha-chymotrypsin and hyaluronidase;
  - chelating agents such as ethylenediaminetetraacetic acid (EDTA) and deferoxamine;
  - immunosuppressants and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine and combinations of the compounds mentioned above, such as antibiotics/antiinflammatories combinations such as the combination of neomycin sulfate and dexamethasone sodium phosphate and combinations concomitantly used for treating glaucoma, for example, a combination of timolol maleate and aceclidine.

In general the drug delivery composition of the present invention will contain from about 0.01% to about 60% by weight of the medicament or pharmaceutical, from about 1% to about 50% of the polymer, the above amounts of ionic polysaccharide, and the balance water. In special situations, however, the amounts may be varied to increase or decrease the dosage schedule.

If desired, the ophtnalmic drug delivery vehicle, laser ablatable corneal mask, and corneal protective compositions of the invention may also contain preservatives, cosolvents, suspending agents, viscosity enhancing agents, ionic-strength and osmolality adjustors and other excipients in

addition to the medicament and buffering agents. Suitable water soluble preservatives which may be employed in the invent ire drug delivery vehicle are sodium bisulfite, sodium thiosulfate, ascotbate, benzalkonium chloride, chlorabutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol phenylethanol and others. These agents may be present, generally, in amounts of about 0.001% to about 5% by weight and, preferably, in the amount of about 0.01 to about 2% by weight.

Suitable water soluble buffering agents are alkali or alkali earth carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and the like, such as sodium phosphate, citrate, borate, acetate, bicarbonate, carbonate and tromethamine (TRIS). These agents are present in amounts sufficient to maintain the pH of the system at 7.4±0.2 and preferably, 7.4. As such the buffering agent can be as much as 5% on a weight basis of the total composition.

Representative buffering agents or salts useful in maintaining the pH at about 7.4±0.2 are alkali or alkali earth carbonates, chlorides, sulfates, phosphates, bicarbonates, citrates, borates, acetates and succinates. Representative preservatives are sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol and phenylethanol.

The corneal mask compositions of the invention are an improvement over the prior art thermo-reversible gels containing a polyoxyalkylene polymer as the sole polymer, in that the compositions of the invention provide greater gel strength because they are more resistant to shear thinning and are characterized as thermally-irreversible. These advantages are obtained by the incorporation of an ionic polysaccharide in admixture with a water soluble, film forming polymer. They can be optimized for optimum physiological tolerance in the eye by formulating the compositions so as to have a neutral pH and isotonic characteristics. These former advantages are obtained by the incorporation of an ionic polysaccharide in admixture with a water soluble, film forming polymer. By matching the osmolality and pH of the laser ablatable corneal mask compositions of the invention to those of the lacrimal fluid of the eye, it is possible to eliminate burning or other discomfort upon application of the corneal mask of the invention to the eye. The higher gel strength compositions upon contact with a counter-ion allow retention of the gel as an in situ formed corneal mask for long intervals.

The preparation of the drug delivery compositions, corneal protective compositions, and ablative corneal shield compositions of the invention is described below. The Examples which follow were prepared, generally, in accordance with the following preparation procedure. A mixture of a water soluble, film forming polymer and ionic polysaccharide is stirred or shaken in admixture with the aqueous buffer solution to bring about a more rapid solution of the polymer. The pharmacologically active medicaments and various additives such as salts and preservatives can subsequently be added and dissolved. In some instances the pharmacologically active substance must be suspended since it is insoluble in water. The pH of 7.4±0.2 is obtained by of appropriate buffering agents.

The following Examples illustrate the various aspects of the invention but are not intended to limit its scope. Where not otherwise specified throughout this specification and claims, temperatures are given in degrees centigrade and parts, percentages, and proportions are by weight.

EXAMPLE 1

In this Example there is described a composition of the invention suitable for ophthalmic use as a laser ablatable

corneal mask or protective corneal shield. The composition was characterized as iso-osmotic and neutral in pH. An aqueous solution was made by dissolving the hydroxypropyl methyl cellulose in aqueous buffer solution together with the sodium alginate. The hydroxypropyl methyl cellulose was characterized as grade F50LV Premium, obtained from The Dow Chemical Company. The sodium alginate, characterized as high viscosity grade HF120 was obtained from Protan, Inc. The proportions of ingredients in percent by weight are as follows:

Hydroxypropyl methyl cellulose	2.0
Sodium Alginate, high viscosity	1.0
Glycerin	0.25
Boric acid-sodium borate buffer	96.75

The boric acid-sodium borate buffer was prepared as follows: In a two liter volumetric flask, 24.7 grams of boric acid and 3.8 grams of sodium borate decahydrate were dissolved in two liters of purified water, USP. The formulation of this Example had a measured pH of 7.2 and an osmolality of 277 mOsm/Kg. A small amount of the formulation was placed on a glass slide and evenly spread so as to create a thin film. The film was subsequently sprayed with an aqueous solution of calcium chloride having a concentration of 2% to about 5% by weight. The film was characterized as strong, transparent, and resembled a thin, soft hydrophilic corneal contact lens which would be useful as a protective corneal mask or as an ablatable mask useful in laser keratectomy.

The product was further characterized by measuring the average penetration in millimeters determined using a Precision Penetrometer with a ¼ size (9.38 grams, ASTM D-1043) cone and plunger. The penetration of the aqueous solution of polymers prepared above was greater than 20 mm. Subsequent to treatment of this solution with a few drops of a 2%–5% by weight aqueous solution of calcium chloride, a gel was formed in which the penetration was reduced to 5 mn.

EXAMPLES 2 AND 3

In these Examples there are described compositions of the invention for ophthalmic use as a corneal protective mask or as a laser ablatable corneal mask. Utilizing the same procedure as described in Example 1, an aqueous composition containing sodium hyaluronate and sodium alginate was prepared in two separate compositions. Sodium hyaluronate is commercially available from Meiji Seika Inc. Example 2 was hypoosmotic having an osmotic pressure of 249 mOsm/Kg and Example 3 was hyperosmotic having an osmotic pressure of 319 mOsm/Kg. Both compositions were characterized as neutral in pH. The formulations have the following proportions by weight:

	Example 2	Example 3
Sodium hyaluronate	1.0	1.0
Sodium alginate, high viscosity	1.0	1.0
Glycerin	—	0.5
Boric acid-sodium borate buffer	98.0	97.5

These compositions were evaluated as described in Example 1 by spreading a small amount of the formulation on a glass slide and subsequently spraying the coated slide with a 5% by weight aqueous solution of calcium chloride. Similar strong, transparent, soft films were obtained which

would be useful as a protective corneal shield or as a laser ablatable corneal mask.

Example 3 was further characterized by measuring the average penetration in millimeters determined using a Precision Penetrometer with a ¼ size (9.38 grams, ASTM D-1043) cone and plunger. The penetration of the aqueous solution of polymers prepared adore was greater than 20 mm. Subsequent to treatment of this solution with a few drops of a 2%–5% by weight aqueous solution of calcium chloride, a gel was formed in which the penetration was reduced to 5.9 mn.

EXAMPLE 4

In this Example there is described a composition of the invention for ophthalmic use as a protective corneal shield or a laser ablatable corneal mask. An aqueous mixture comprising polyvinyl pyrrolidone and sodium alginate, high viscosity was prepared as follows: The percentages below are by weight.

Polyvinyl pyrrolidone	0.8
Sodium alginate, high viscosity	1.0
Glycerin	0.3
Boric acid-sodium borate buffer	97.9

The composition was characterized as neutral in pH having a pH of 7.2. The composition was hypoosmotic having an osmolality of 270 mOsm/Kg.

The product was further characterized by measuring the average penetration in millimeters determined using a Precision Penetrometer with a ¼ size (9.38 grams, ASTM D-1043) cone and plunger. The penetration of the aqueous solution of polymers prepared above was greater than 20 mm. Subsequent to treatment of this solution with a few drops of a 5% by weight aqueous solution of calcium chloride, a gel was formed in which the penetration was reduced to 4.1 mm.

EXAMPLE 5

In this Example there is described a composition of the invention for ophthalmic use as a laser ablatable mask or as a protective corneal shield. In accordance with the procedure of Example 1, chondroitin sulfate and sodium alginate were prepared as an aqueous solution utilizing the percentages by weight indicated below.

Sodium Chondroitin sulfate	2.0
Sodium alginate, high viscosity	1.0
Glycerin	0.3
Boric acid-sodium borate buffer	96.7

The aqueous solution was characterized as neutral in pH having a pH of 7.0. The aqueous solution was hyperosmotic having a measured osmolality of 354 mOsm/Kg. The penetration utilizing a Precision Penetrometer with a ¼ size cone, as described above, was greater than 20 mm prior to treatment with a few drops of a 2%–5% aqueous solution of calcium chloride. Subsequent to treatment with the aqueous calcium chloride solution, a gel was formed in which the penetration was reduced to 5.1 mm.

EXAMPLES 6–10

Ion exchange resin beads sold under the trade name Duolite were treated so as to incorporate calcium by first treating a 30 gram sample of the ion exchange resin with a solution of 0.1 molar hydrochloric acid so as to allow for the exchange of protons for sodium. After three washings with 0.1 molar hydrochloric acid, the beads were washed with water and then washed twice with a 2% aqueous solution of calcium chloride. Each of the washing steps took place over a period of 16 hours (overnight). The beads were thereafter filtered and washed with water utilizing coarse filter paper and a Buchner glass filter assembly. The beads were then left overnight in a desiccator to dry. The dried beads of ion exchange resin which were obtained are utilized in the amount of 2 grams to fill a first compartment (close to the needle of the syringe) of a glass syringe utilized to apply liquids and dry materials. The syringe is sold under the tradename Hypak. Into the second compartment of the syringe, there is placed successively the solutions of Examples 1–5. Pushing the plunger of the syringe forward results in mixing the solution of Examples 1–5 with the ion exchange beads. After 5 to 10 minutes subsequent to mixing, the mixture is expelled from the syringe. After an additional 15 minutes the expelled material forms (without drying) a strong, transparent gel on the substrate on which it is expelled.

EXAMPLES 11–15

These examples describe the successive application of an aqueous solution of Examples 1 and 3–5 to the cornea of a rabbit eye and the conversion of the aqueous liquid to a gel by the application of a 10% calcium chloride solution having a pH of 6.9. The calcium chloride solution is applied to the concave surface of a contact lens prior to contacting the surface of the aqueous liquid coating applied upon the cornea of the rabbit eye. After applying the compositions of Examples 1 and 3–5 to the cornea of a rabbit while placed under general anesthesia, a liquid coating is formed upon the cornea. Subsequently, a 10% aqueous solution of calcium chloride is applied to the concave surface of a hard contact lens and the contact lens is placed over the coating on the cornea of the rabbit eye. The time required for the formation of a gel is less than 5 minutes. Thereafter, the contact lens is removed to expose a perfectly smooth and optically clear gelled surface of the composition of Examples 1 and 3–5. Excimer laser keratectomy is thereafter performed utilizing an argon fluoride excimer laser (193 nm). Further details of the excimer laser keratectomey process can be found in *Archives of Ophthamology*, vol. 106, Feb., 1988, entitled "Excimer Laser Keratectomy with a Rotating-slit Delivery System", Hanna et al, incorporated herein by reference.

EXAMPLES 16–18

These Examples describe drug compositions of the invention suitable for ophthalmic use in comparison with Control Examples in in-vitro tests for drug release.

EXAMPLE 16 CONTROL—Forming no part of this invention

	Percentage by weight
Timolol maleate	0.50
Poloxamer 407	16.00
Sodium phosphate, monobasic, monohydrate	0.15
Sodium phosphate, dibasic	0.63
Glycerin	0.75
Sterile water	81.97

An eye drop or medicated contact lens composition was prepared using a suitable glass container in which the sodium phosphate salts and glycerin were dissolved in sterile water. The polymer was next mixed with the buffer solution at 65° C. for 1 hour, followed by a further 2–3 hours in cold conditions. To a fixed weight of the polymer solution was added and dissolved, an accurate amount of timolol maleate (Huhtamaki OY Pharmaceuticals, Turku, Finland) to make a 0.5% w/w concentration.

EXAMPLE 17 CONTROL—Forming no part of this invention

	Percentage by weight
Timolol maleate	0.50
Poloxamer 407	17.00
Sodium alginate, high viscosity	1.50
Sodium borate, decahydrate	0.16
Boric acid	1.00
Glycerin	0.30
Sterile water	81.27

A medicated contact lens was prepared using a suitable glass container in which the sodium borate, boric acid and glycerin we re dissolved in sterile water. Sodium alginate was sprinkled in with stirring to form a uniform paste. The polymer was next mixed with this mixture at 65° C. for 1 hour, and for a further 2–3 hours under cold conditions. To a fixed weight of the polymer-alginate solution, was added and dissolved, an accurate amount of timolol maleate (Huhtamaki OY Pharmaceuticals, Turku, Finland) to make a 0.5% w/w concentration.

EXAMPLE 18

	Percentage by weight
Timolol maleate	0.50
Sodium hyaluronate	1.00
Sodium alginate, high viscosity	1.00
Sodium borate, decahydrate	0.19
Boric acid	1.21
Glycerin	0.50
Sterile water	95.60

A medicated contact lens was prepared using a suitable glass container in which the sodium borate, boric acid and glycerin were dissolved to make a solution in sterile water. Sodium alginate and sodium hyaluronate were sprinkled into this solution with continuous stirring to form a uniform paste. To a fixed weight of the hyaluronate-alginate mixture, there was added and dissolved an amount of timolol maleate (Huhtamaki OY Pharmaceuticals, Turku, Finland) to make a 0.5% w/w concentration.

An in-vitro evaluation of the contact lens of Examples 16–18 was carried out as follows: The medicated contact lens was prepared by accurately weighing a big drop of the formulation on a glass microscopic slide (2"×1"). Two drops of a 5% by weight calcium chloride counter-ion solution was next placed on the formula drop. After 1 minute, the excess calcium chloride was blotted away from the now formed corneal contact lens.

The glass slide with contact lens in place was next placed at the bottom of the 1 liter dissolution vessel containing 500 ml of purified water, maintained at 37° C. The dissolution experiment was carried out as per method 2 (paddle) of the United States Pharmacopoeia XXII, page 1579, The United States Pharmacopoeial Convention, Mack Publishing Company, 1990. Paddle stirring rate was 50 revolutions per minute.

At regular time intervals, aliquots were removed from the vessels for analysis by High Pressure Liquid Chromatography. Six vessels were used for each formulation (n=6).

TIMOLOL MALEATE DELIVERY FROM CORNEAL LENSES n = 6

	CUMULATIVE % OF TIMOLOL RELEASED (SD)				
TIME	Example 16	Example 17		Example 18	
0	0.0	0.0		0.0	
10 min	100.0	—		—	
30 min	100.0	—		—	
60 min	100.0	80.3	(12.0)	77.9	(6.2)
120 min	—	90.0	(3.8)	93.9	(2.2)
240 min	—	95.1	(6.1)	95.9	(1.3)
360 min	—	90.1	(3.1)	94.9	(2.5)
480 min	—	95.7	(3.3)	97.5	(2.9)

It was observed that the drug is released in-vitro, by diffusion and not by the erosion of the lens. Approximately 80% of timolol maleate is released in 1 hour and the remaining amount gradually diffuses out in 3 to 4 hours. The lenses remained intact 48 hours after the start of the experiment. On the other hand, when 0.9% sodium chloride was used in place of purified water as the dissolution medium, the drug was released by both erosion and diffusion, within the first hour. The lenses are first reduced in size and then dissolved away within 6 hours. This erosion is dependent on the replacement of calcium ions (in the lens) with sodium ions (from the dissolution medium). The break up in-vivo is expected to be slow and gradual and is dependent on the sodium concentration in the tear fluid.

In the following examples there are described compositions having multiple uses. For instance, they may be used as vehicles for drug delivery by topical application or by injection or useful as a protective corneal shield or in a process for excimer laser keratectomy as a laser ablatable corneal mask.

The procedure for preparation and the polymeric materials utilized in the composition are those described in Example 1. The TRIS-hydrochloride buffer utilized in this composition was prepared utilizing the ingredients and proportions by weight indicated below.

TRIS (tromethamine, USP)	0.6058
Concentrated hydrochloric acid	0.4123
Purified water, USP	100

The composition was found to have a pH of 7.4 and an osmolality in mOsm/kg of 83. The procedure for preparation of this buffer is as follows: The weighed amount of TRIS was placed in a 2-liter volumetric flask and about 1 liter of purified water was added to the flask. The concentrated hydrochloric acid was added and the solution was made up to volume by adding the remaining water in the formulation.

The calcium based counter-ion solution utilized to gel the inventive drug delivery compositions of Examples 19–22 was prepared utilizing the following proportions of ingredients in proportions by weight.

Calcium chloride, dihydrate	1.2
Calcium gluconate, anhydrous	3.0
Purified water, USP	100.0

The composition had a pH of 6.88 and an osmolality in mOsm/kg of 299. The calcium based counter- ion solution

was prepared as follows: The calcium gluconate and calcium chloride in the required amount were placed in a 200 ml volumetric flask. Approximately 100 ml of water were added to partially dissolve the salts. The solution was, thereafter, warmed to 80° C. to facilitate disolution. The solution was cooled and the remaining water was added to make up to 200 ml volume.

EXAMPLE 19

A composition containing both sodium alginate and sodium hyaluronate was prepared for use as a vehicle for drug delivery, a laser ablatable corneal mask, a protect ire corneal shield, or a composition for use in preventing post-surgical adhesions. The proportions by weight are as follows:

Sodium hyaluronate	0.5
Sodium alginate	1.0
Sodium chloride	0.54
TRIS-hydrochloride Buffer	97.96

The composition was found to have a pH of 7.6 and an osmolality of 297 mOsm/kg prior to treatment with calcium ions by the addition of the previously described calcium based counter-ion solution. After treatment with calcium ions the osmolality was 302 mOsm/kg.

The product was further characterized by measuring the average penetration in millimeters as determined using a precision penetrometer with a ¼ size (9.38 grams, ASTM D-1043) cone and plunger. The penetration in millimeters prior to treatment of the composition of Example 19 with calcium ions was greater than 20 mm. After treatment with calcium ions the penetration was 4.77 mm.

EXAMPLE 20

A composition containing polyvinyl pyrrolidone and sodium alginate was prepared which is useful for the same applications as that formulation described in Example 19. The proportions in percent by weight of the ingredients of the composition are as follows:

Polyvinyl pyrrolidone	0.8
Sodium alginate	1.0
Sodium chloride	0.62
TRIS-hydrochloride buffer	97.58

The composition had a pH of 7.59 and an osmolality in mOsm/kg prior to treatment with calcium ions of 320 and after treatment with calcium ions of 289. The penetration utilizing a precision penetrometer as further described in Example 19 was greater than 20 prior to treatment of the composition with calcium ions and 6.57 after treatment with calcium ions.

EXAMPLE 21

A composition useful for the same uses as stated in Example 19 containing a combination of sodium alginate and chondroitin sulfate was prepared.

The proportions of ingredients in percent by weight are as follows:

Sodium chondroitin sulfate	2.0
Sodium alginate	1.0
Sodium chloride	0.35
TRIS-hydrochloride buffer	96.65

The composition had a pH of 7.9 and an osmolality expressed in mOsm/kg of 301 prior to treatment with calcium ions and 272 after treatment with calcium ions.

The penetration utilizing a precision penetrometer as further described in Example 19 was found to be greater than 20 mm prior to treatment with calcium counter-ions and 4.57 upon treatment with calcium ions utilizing the calcium counter-ion solution prepared above.

EXAMPLE 22

A composition useful for the same uses as stated in Example 19 containing a combination of hydroxypropyl methyl cellulose, and sodium alginate was prepared. The proportions of ingredients and their percent by weight are as follows:

Hydroxypropyl methyl cellulose	2.0
Sodium alginate	1.0
Sodium chloride	0.6
TRIS-hydrochloride buffer	96.4

The composition had a pH of 7.59 and an osmolality expressed in mOsm/kg of 326 prior to treatment with calcium ions and 301 after treatment with calcium ions.

While this invention has been described with reference to certain specific embodiments, it will be recognized by those skilled in the art that many variations are possible without departing from the scope and spirit of the invention, and it will be understood that it is intended to cover all changes and modifications of the invention, disclosed herein for the purposes of illustration, which do not constitute departures from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for forming a protective corneal shield or an ablatable corneal shield or mask in situ comprising administering to the eye of a mammal an aqueous composition capable of being gelled in situ to produce an hyperosmotic, hypoosmotic, or isoosmotic aqueous gel having a controlled pH, said aqueous composition, including at least one film forming polymer; and gelling said film forming polymer in situ to form said protective corneal shield or ablatable corneal shield or mask.

2. The process recited in claim **1**, wherein said aqueous composition further includes at least one ionic polysaccharide.

3. The process recited in claim **2**, wherein said aqueous composition further includes a latent form of a counter-ion capable of gelling said ionic polysaccharide.

4. The process of claim **1**, wherein said film forming polymer is water soluble and is selected from the group consisting of the alkyl celluloses, hydroxyalkyl methyl celluloses, hyaluronic acid, sodium chondroitin sulfate, polyacrylic acid, polyacrylamide, polycyanolacrylates, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, cyclodextrin, polydextrose, dextran, gelatin, polygalacturonic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyalkylene glycols, and polyethylene oxide.

5. The process of claim **2**, wherein said film forming polymer is water soluble and is selected from the group consisting of the alkyl celluloses, hydroxyalkyl methyl celluloses, hyaluronic acid, sodium chrondroitin sulfate, polyacrylic acid, polyacrylamide, polycynaolacrylates, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, cyclodextrin, polydextrose, dextran, gelatin,

polygalacturonic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyalkylene glycols, and polyethylene oxide.

6. The process of claim 3, wherein said film forming polymer is water soluble and is selected from the group consisting of the alkyl celluloses, hydroxyalkyl methyl celluloses, hyaluronic acid, sodium chondroitin sulfate, polyacrylic acid, polyacrylamide, polycyanolacrylates, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, cyclodextrin, polydextrose, dextran, gelatin, polygalacturonic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyalkylene glycols, and polyethylene oxide.

7. The process of claim 1, wherein said film forming polymer is collagen.

8. The process of claim 3, wherein said film forming polymer is collagen.

9. The process of claim 1, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines. decongestants, anti-inflammatories, antiparasitics, miotics, anticholinergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, and muscle relaxants.

10. The process of claim 2, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines, decongestants, anti-inflammatories, antiparasitics, miotics, anticholingertics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives and muscle relaxants.

11. The process of claim 3, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines decongestants, anti-inflammatories, antiparasitics, miotics, anticholingertics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives and muscle relaxants.

* * * * *

polygalacturonic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyalkylene glycols, and polyethylene oxide.

6. The process of claim 3, wherein said film forming polymer is water soluble and is selected from the group consisting of the alkyl celluloses, hydroxyalkyl methyl celluloses, hyaluronic acid, sodium chondroitin sulfate, polyacrylic acid, polyacrylamide, polycyanolacrylates, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, cyclodextrin, polydextrose, dextran, gelatin, polygalacturonic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyalkylene glycols, and polyethylene oxide.

7. The process of claim 1, wherein said film forming polymer is collagen.

8. The process of claim 3, wherein said film forming polymer is collagen.

9. The process of claim 1, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines. decongestants, anti-inflammatorics, antiparasitics, miotics, anticholinergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating

agents, antineoplastics, antihypertensives, and muscle relaxants.

10. The process of claim 2, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines, decongestants, anti-inflammatories, antiparasitics, miotics, anticholingertics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives and muscle relaxants.

11. The process of claim 3, wherein said aqueous composition further contains a drug selected from the group consisting of antibacterials, antihistamines decongestants, anti-inflammatories, antiparasitics, miotics, anticholingertics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives and muscle relaxants.

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United States Patent [19]

Della Valle et al.

[11] **Patent Number:** **5,876,744**

[45] **Date of Patent:** **Mar. 2, 1999**

[54] **HIGHLY BIOADHESIVE AND MUCOADHESIVE COMPOSITIONS CONTAINING POLYVINYL ALCOHOL, POLYCARBOPHIL AND BIOPOLYMER FOR THE TREATMENT OF SKIN CONDITIONS AND AS VEHICLES FOR ACTIVE INGREDIENTS**

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[73] Assignee: **Lifegroup S.p.A.**, Monselice, Italy

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[22] PCT Filed: **Jul. 28, 1995**

[86] PCT No.: **PCT/EP95/02999**

§ 371 Date: **Apr. 22, 1997**

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PCT Pub. Date: **Feb. 15, 1996**

[30] **Foreign Application Priority Data**

Aug. 1, 1994 [IT] Italy MI94A1668

[51] **Int. Cl.**^{6} **A61F 13/00**

[52] **U.S. Cl.** **424/434**

[58] **Field of Search** 424/434

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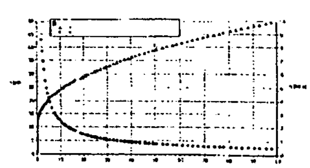
Primary Examiner—Thurman K. Page
Assistant Examiner—Sharon Howard
Attorney, Agent, or Firm—McDermott, Will & Emery

[57] **ABSTRACT**

Compositions having high bioadhesion, mucoadhesion and visoelasticity, containing mixtures of synthetic polymers, such as polyvinyl alcohol and Polycarbophil, and of biopolymers, such as alginic acid, hyaluronic acid and dermatan sulfate, useful in the treatment of skin and mucosal tissues dryness and dehydration, and suitables as vehicles for active ingredients in percutaneous absorption.

15 Claims, 14 Drawing Sheets



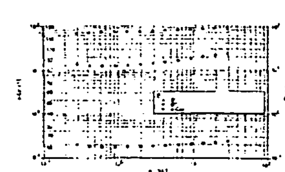


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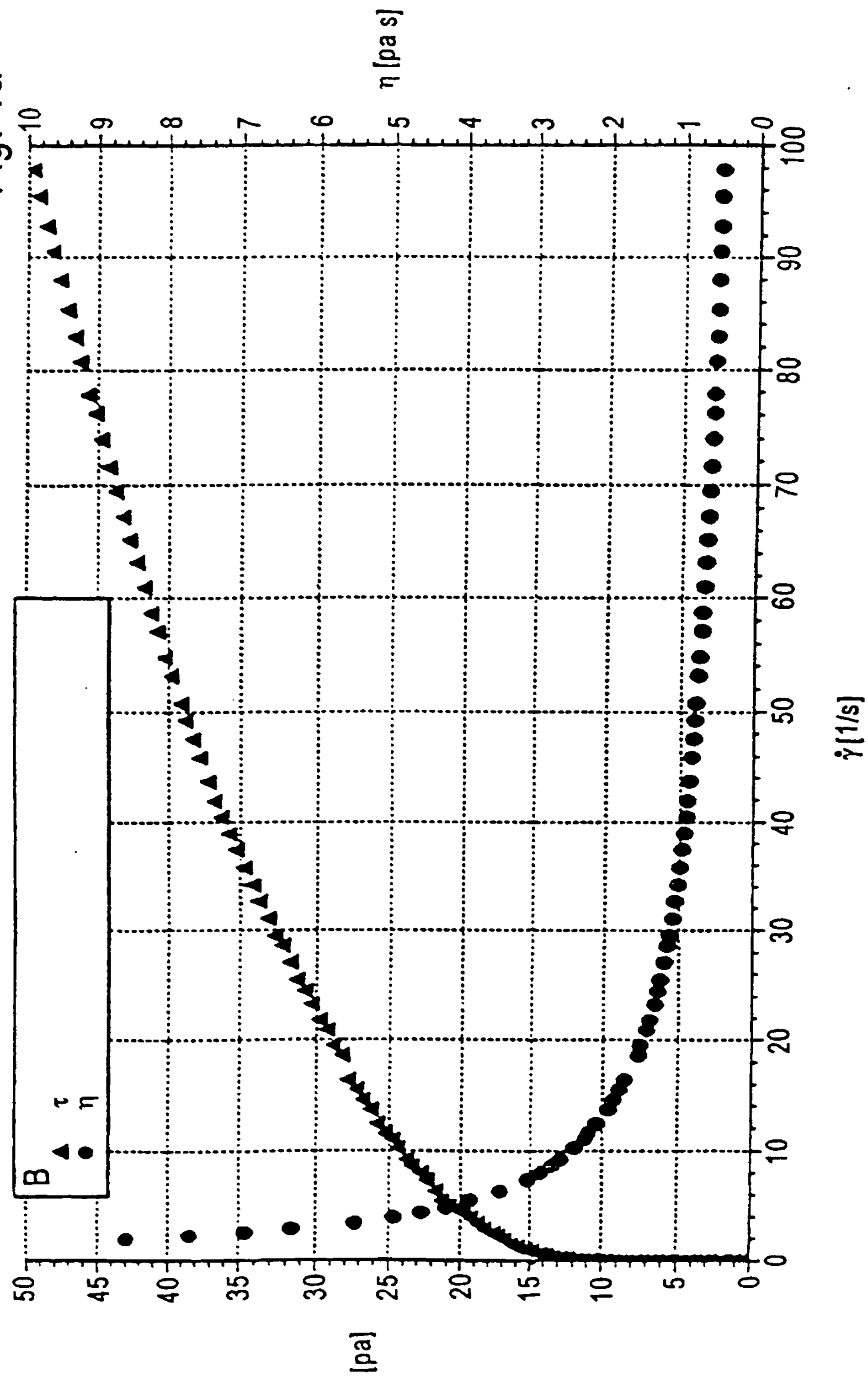
Fig. 1a



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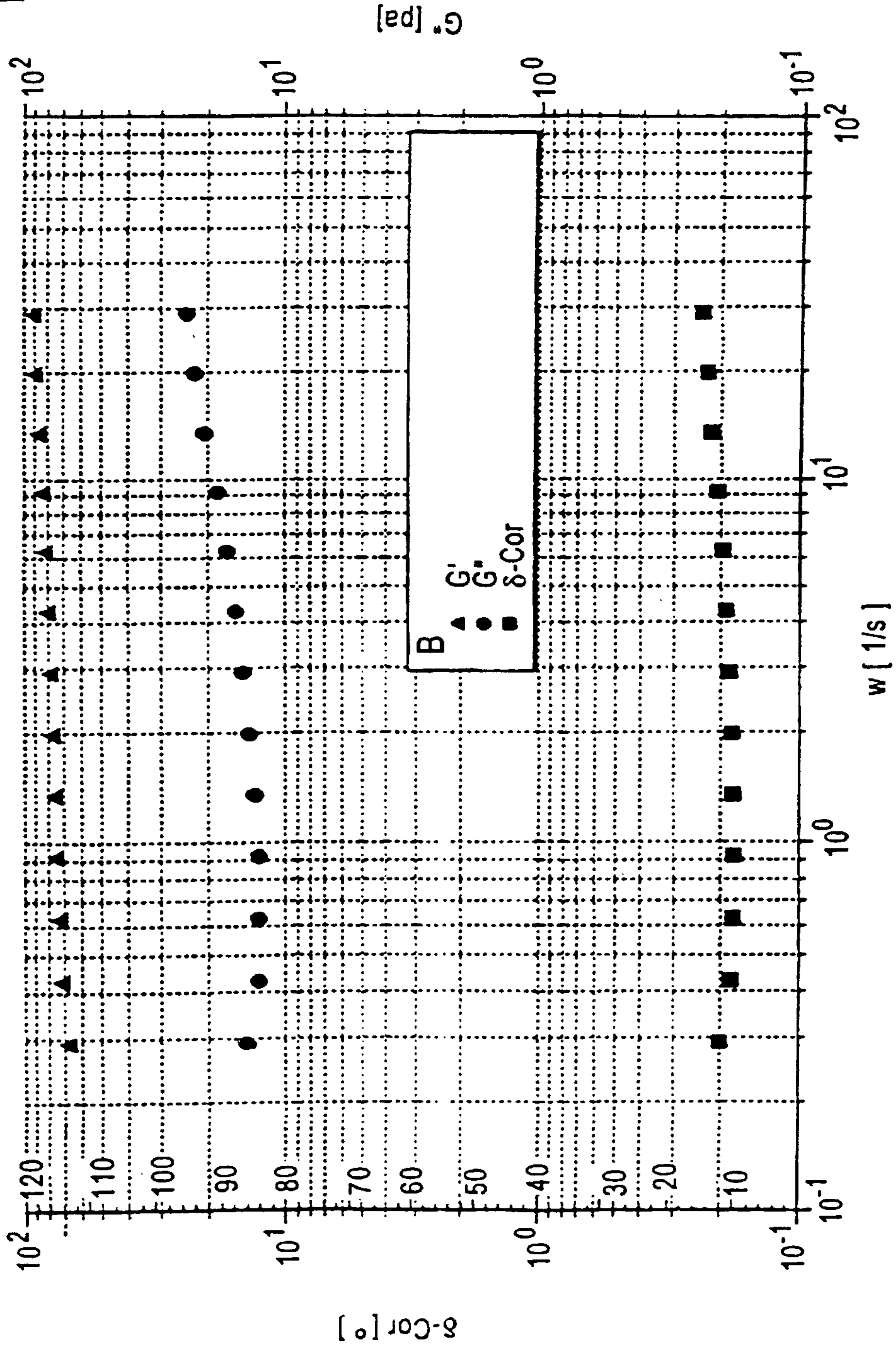
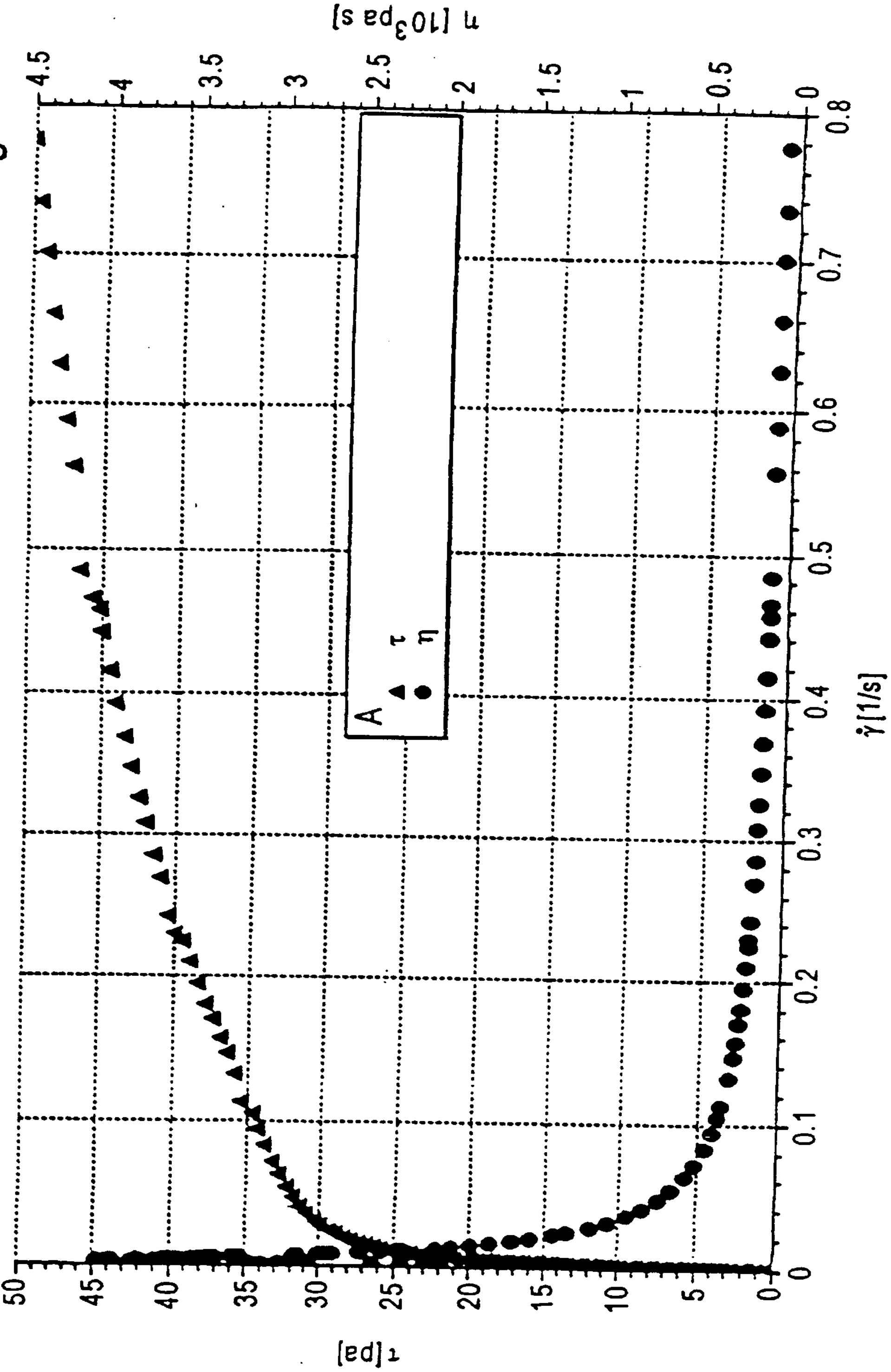


Fig. 2a



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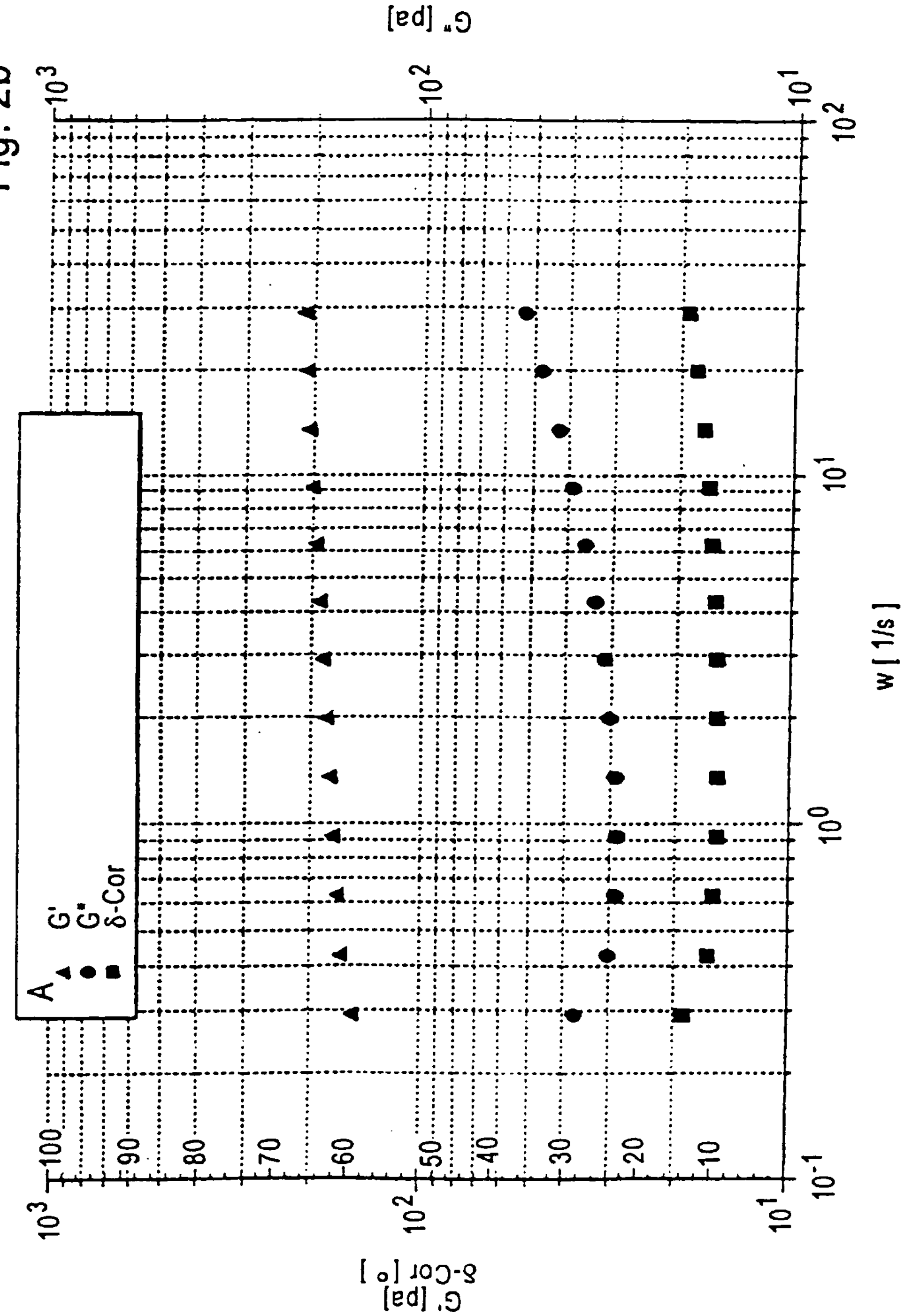


Fig. 3a

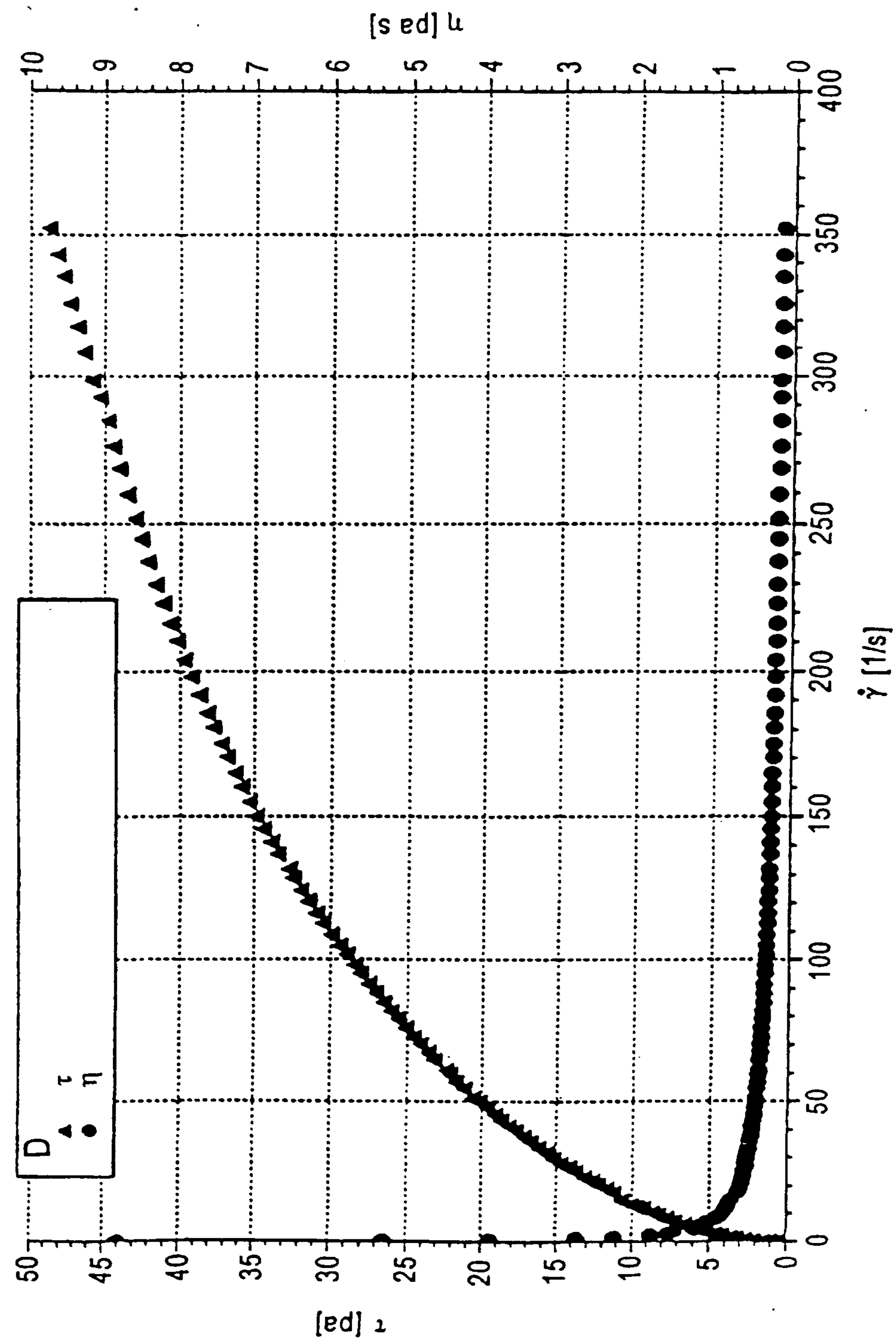
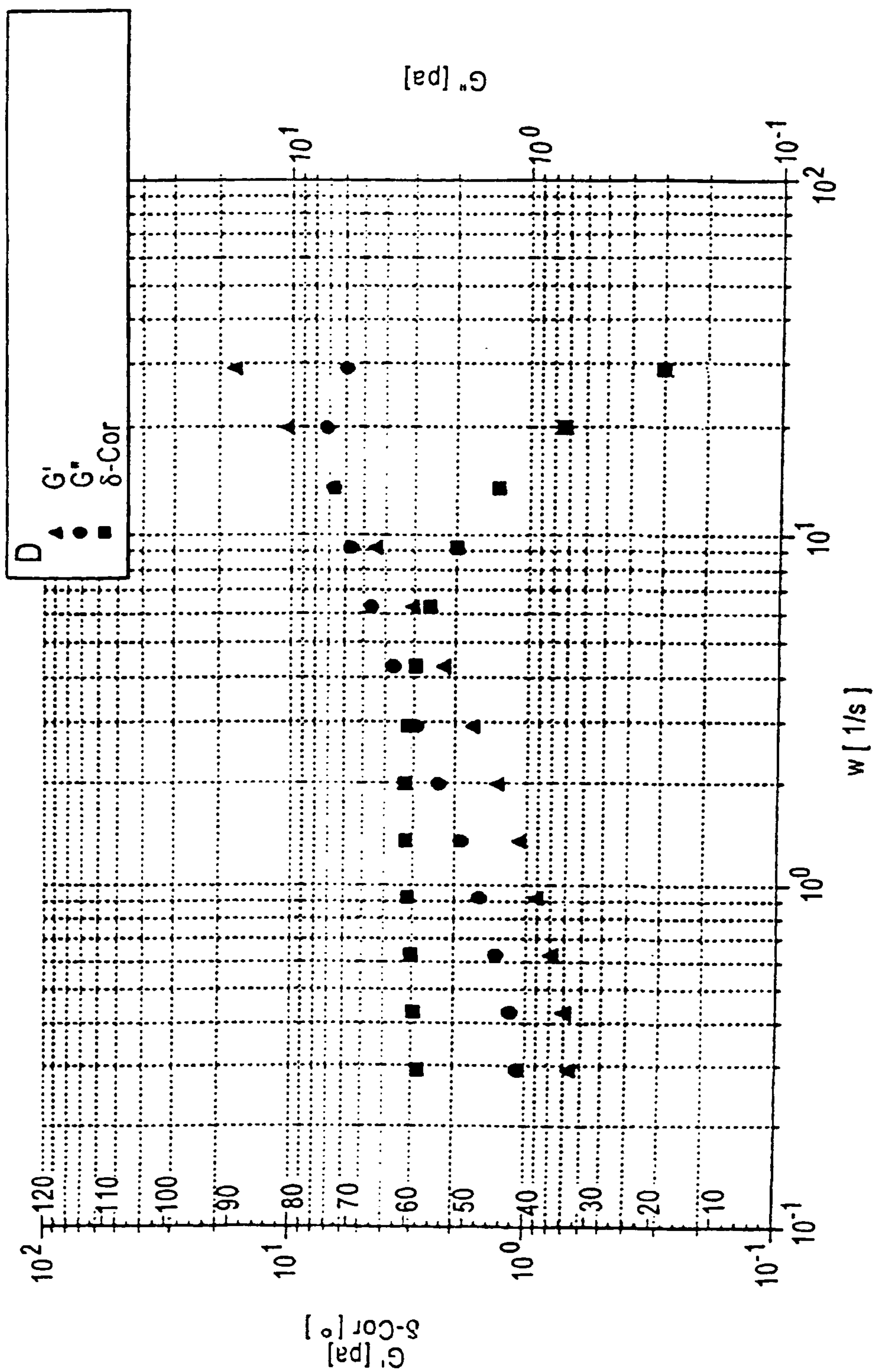
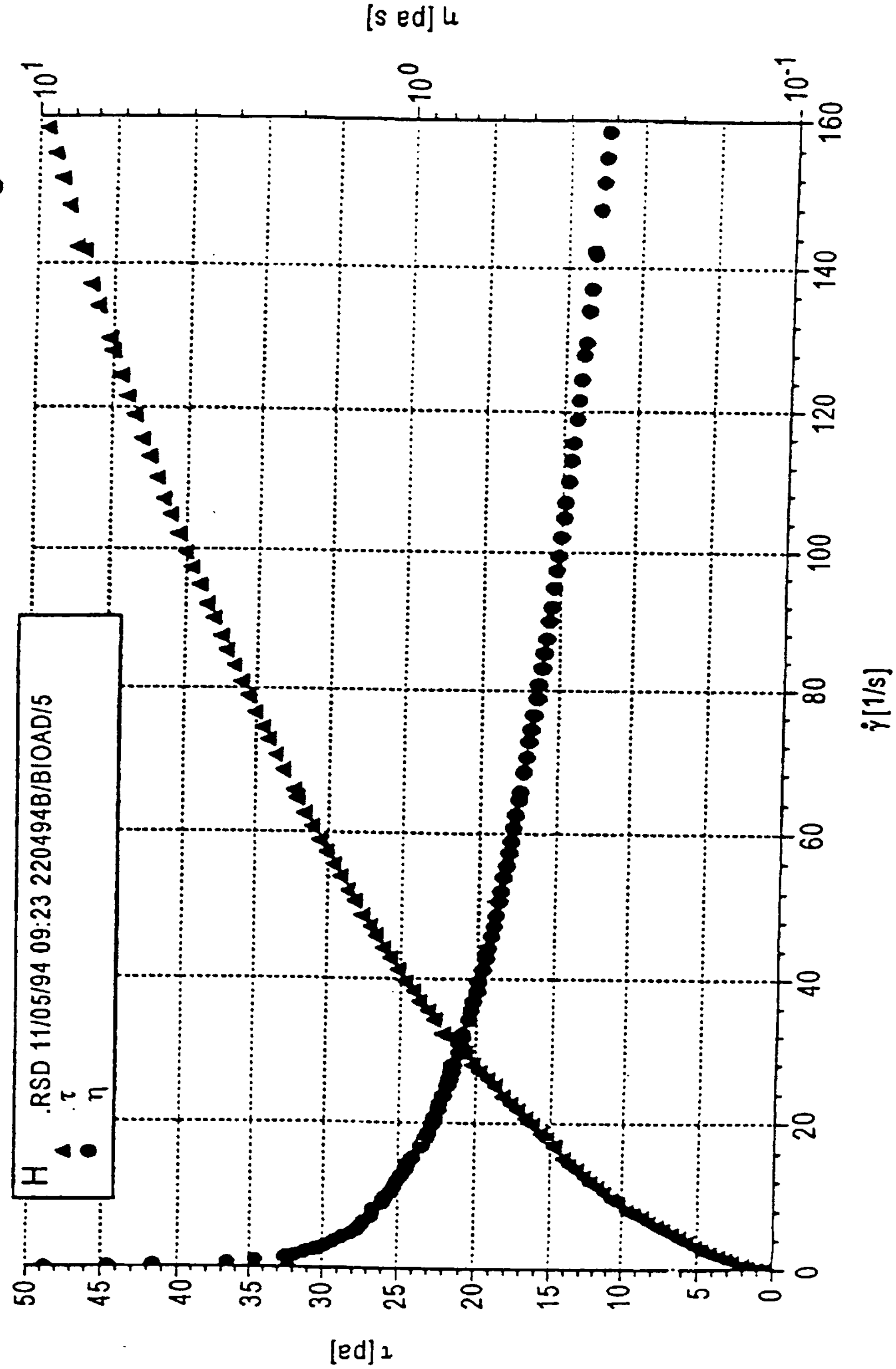


Fig. 3b





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γ̇ [1/s]
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0 5 10 15 20 25 30 35 40 45 50

Fig. 4a

Fig. 4b

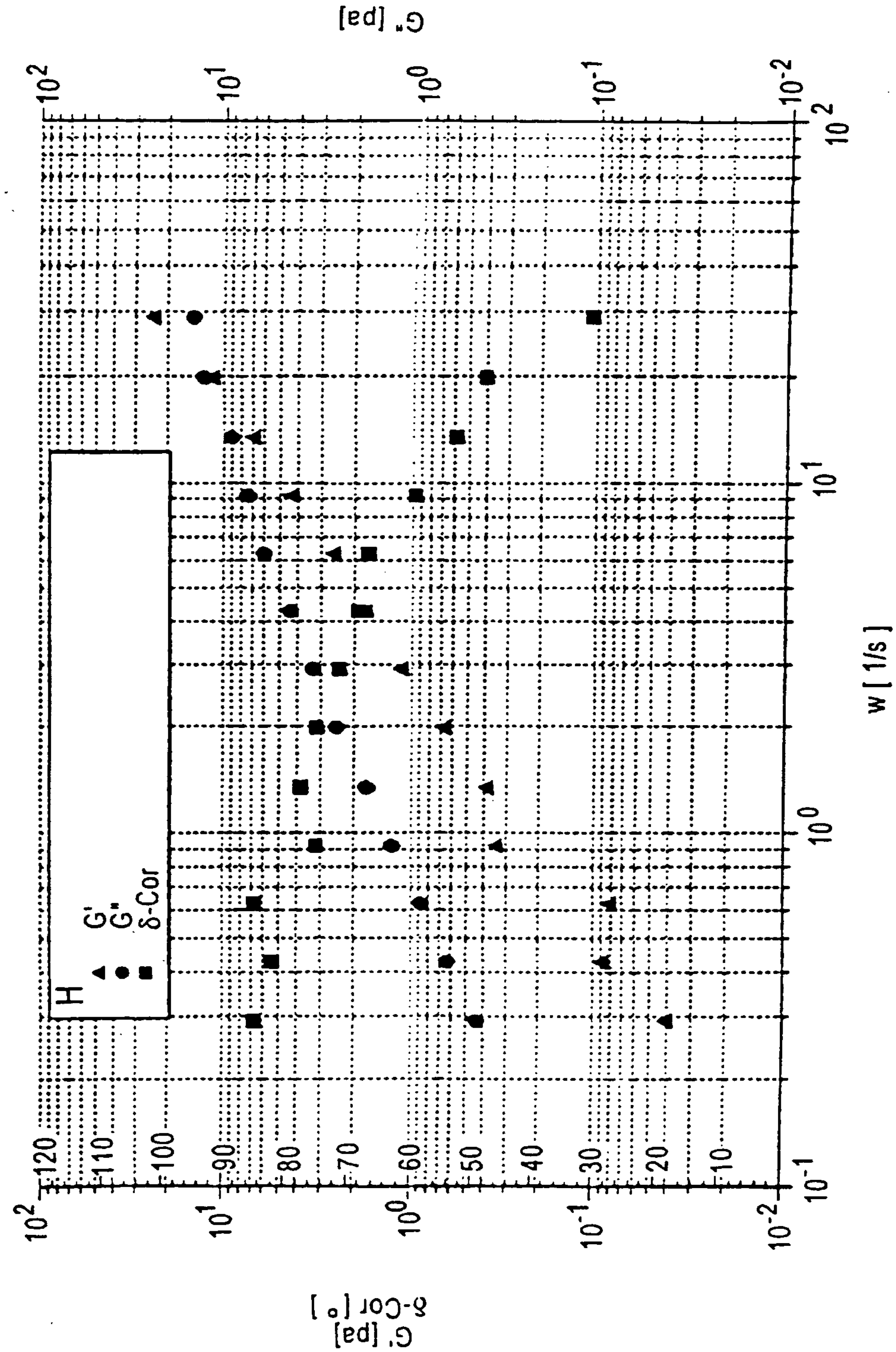

Fig. 5a

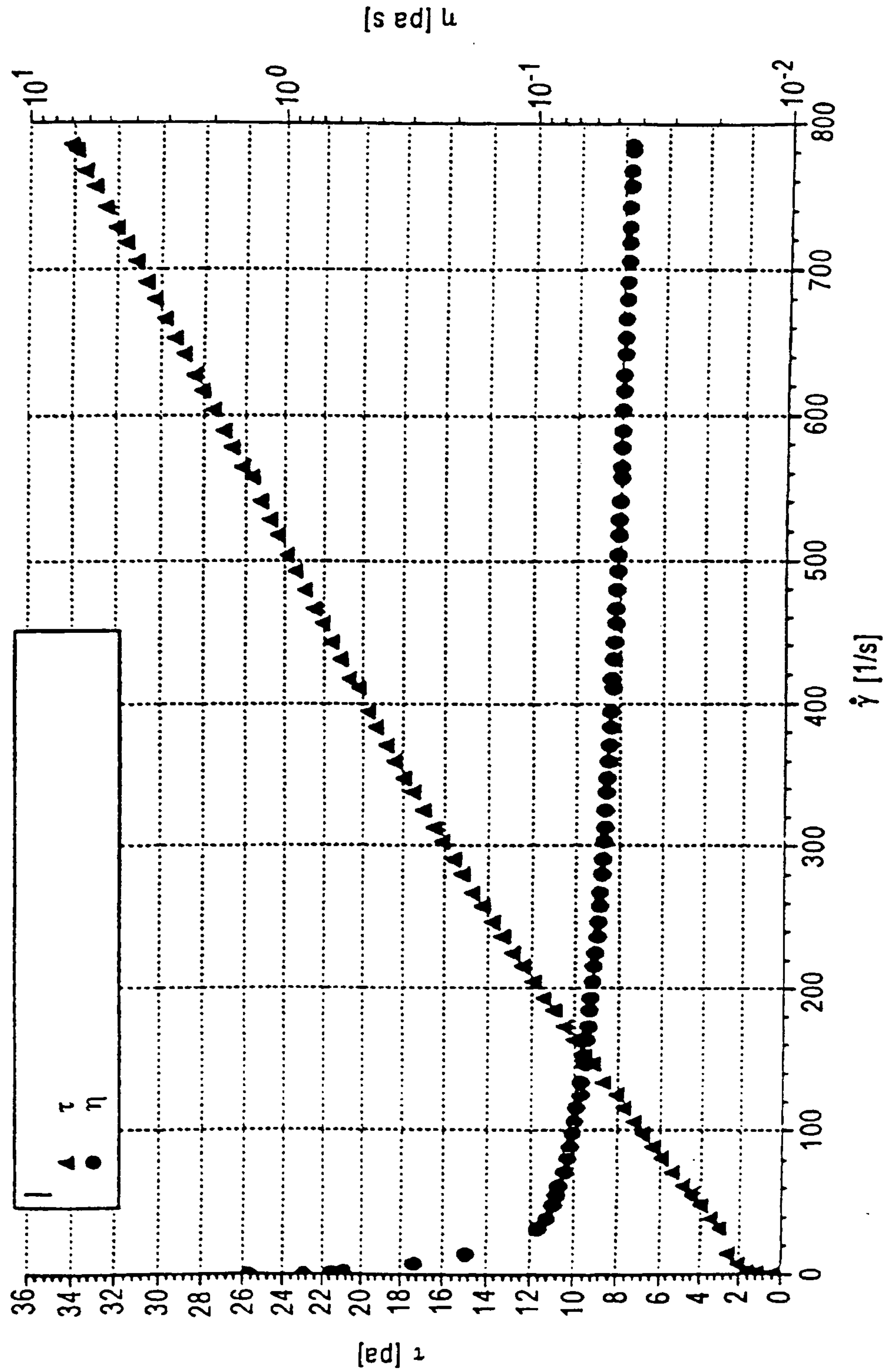
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Fig. 5b

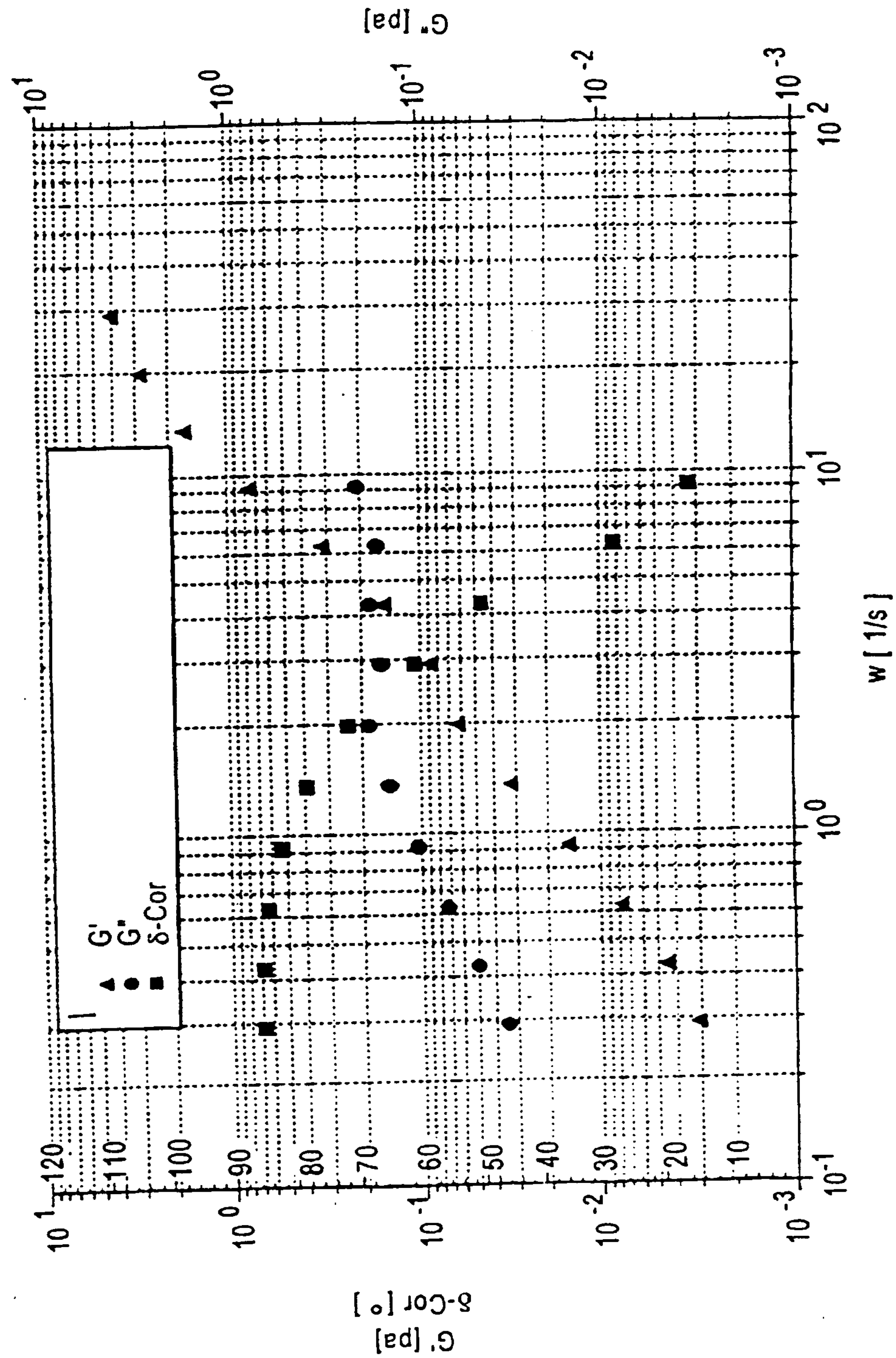

Fig. 6a

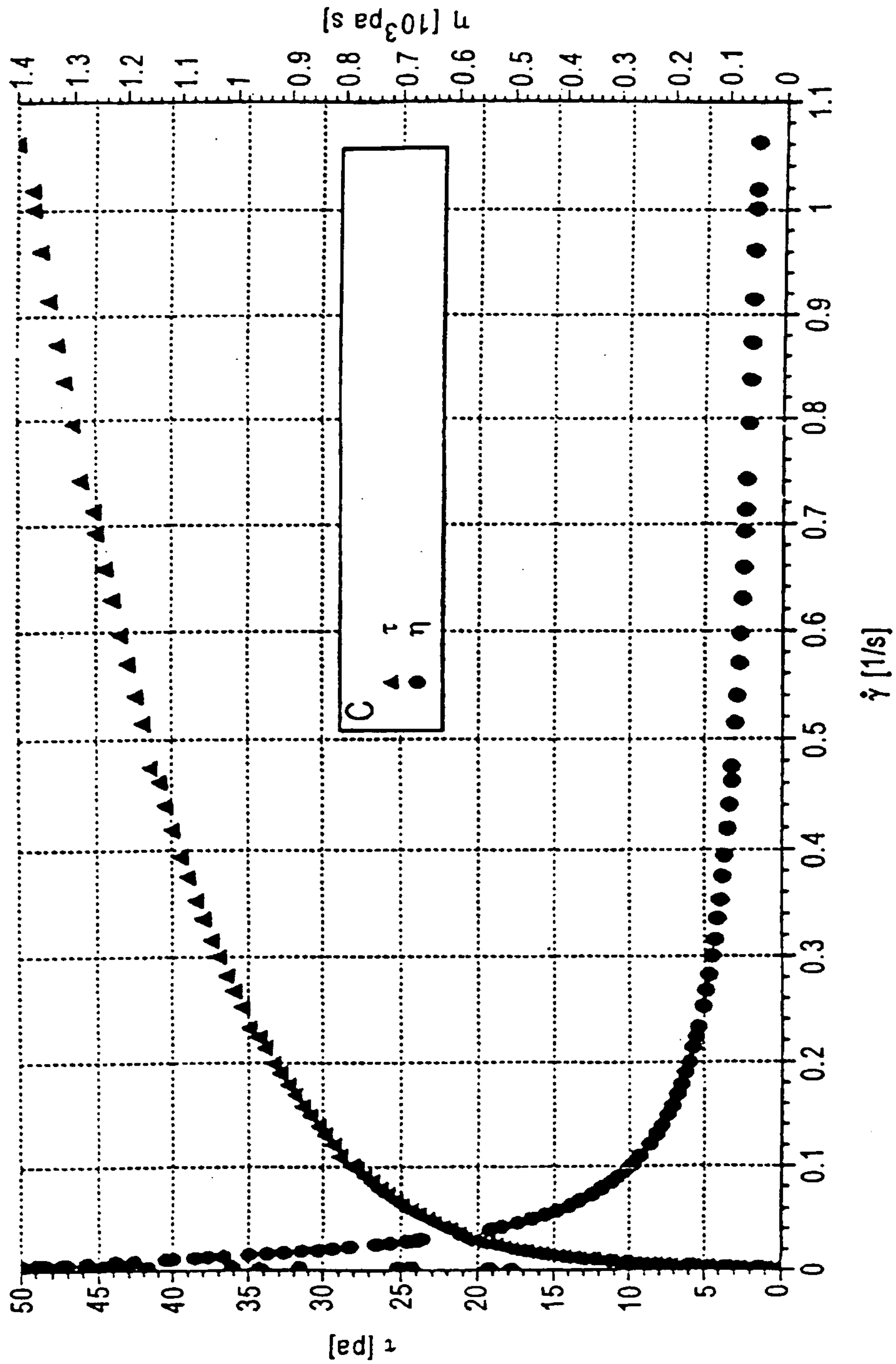
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Fig. 6b

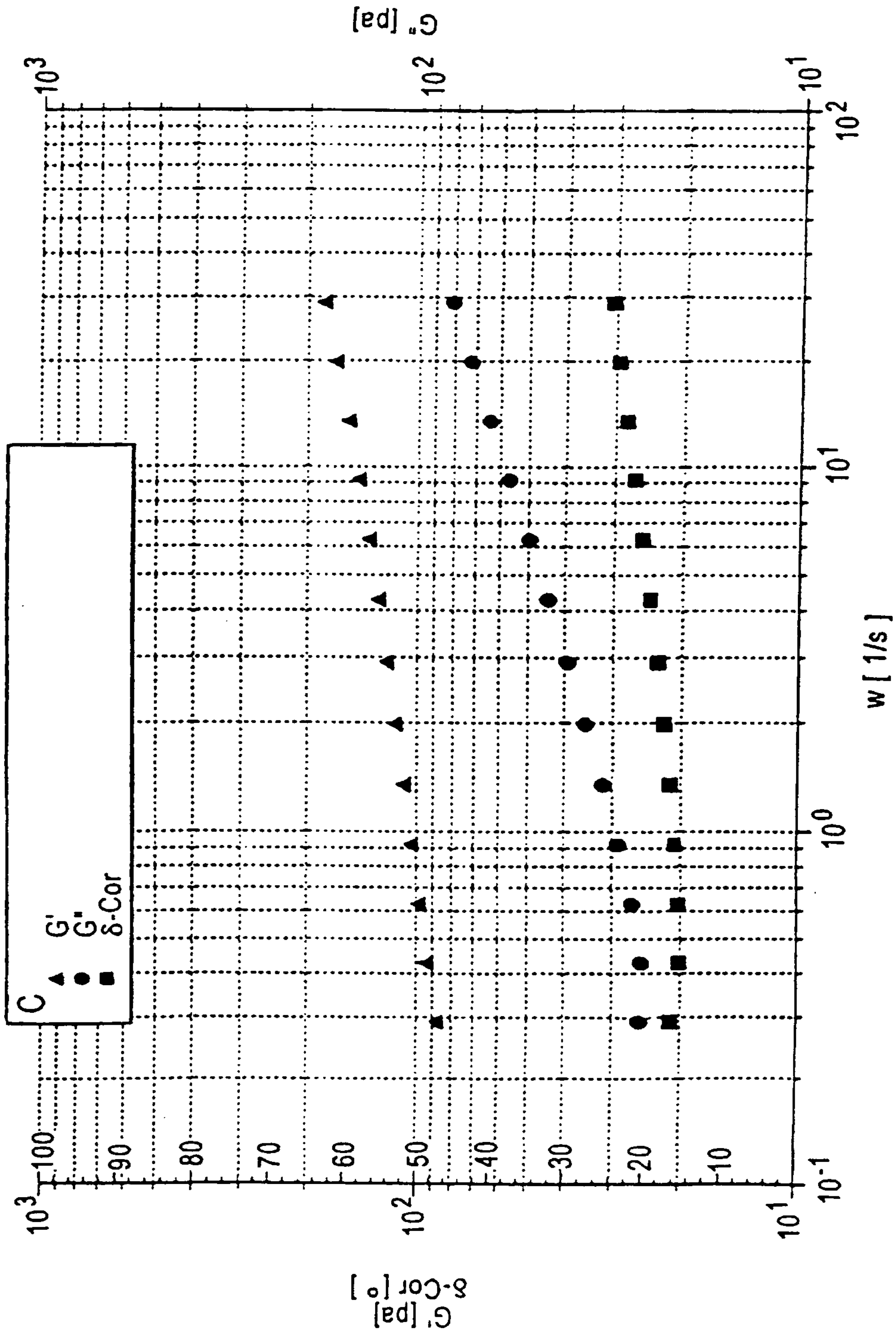

Fig. 7a

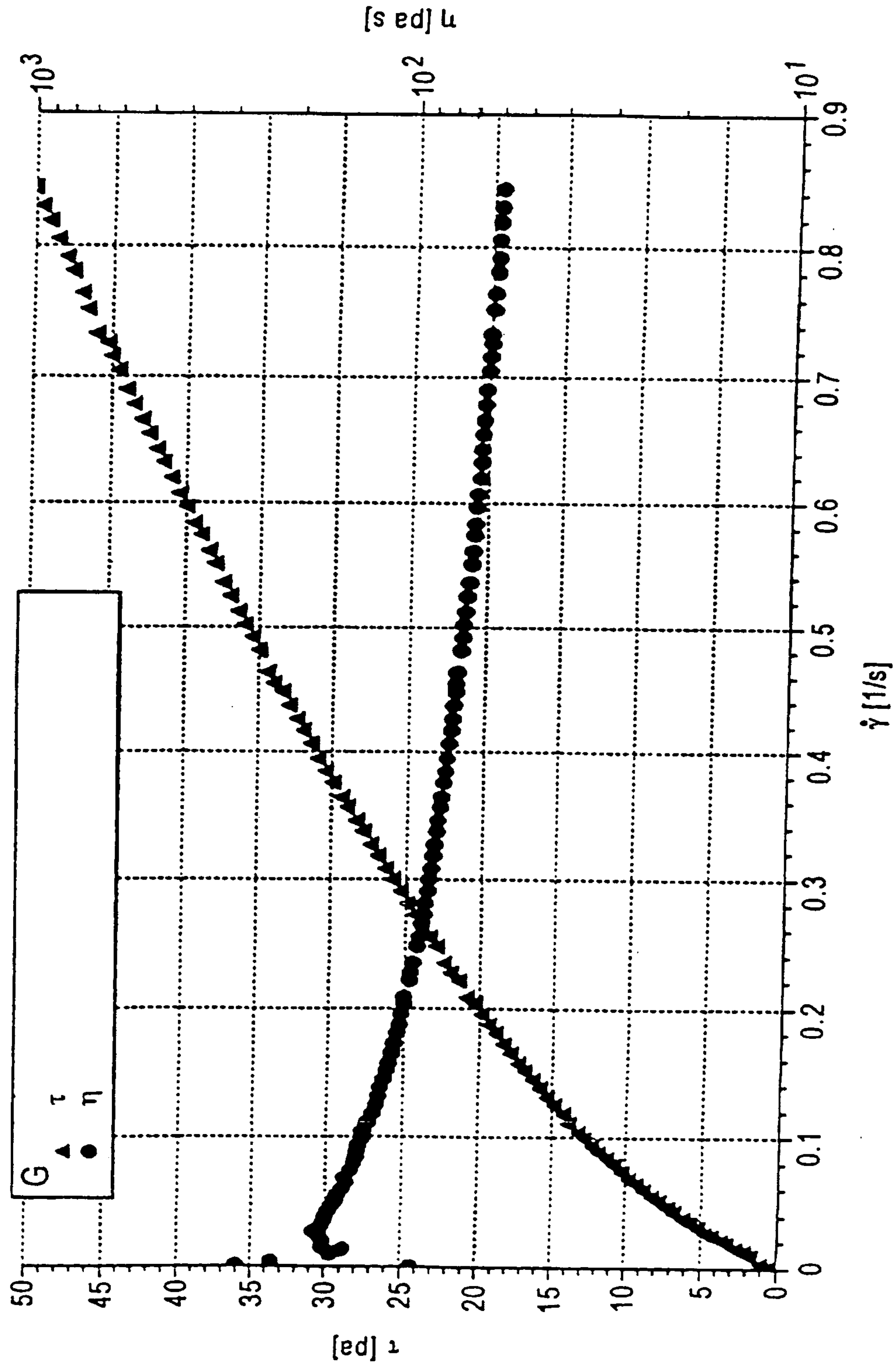
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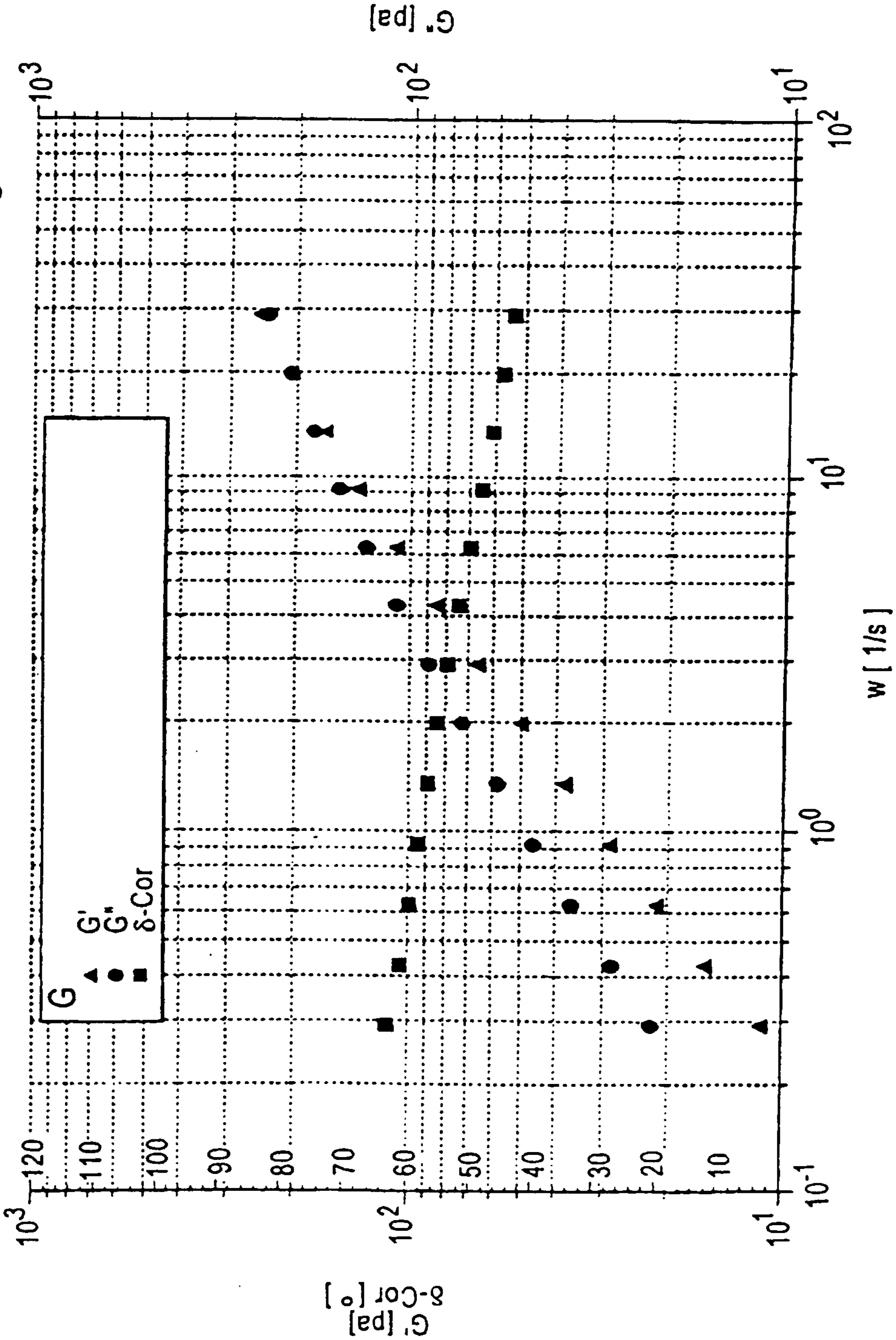
Fig. 7b



HIGHLY BIOADHESIVE AND MUCOADHESIVE COMPOSITIONS CONTAINING POLYVINYL ALCOHOL, POLYCARBOPHIL AND BIOPOLYMER FOR THE TREATMENT OF SKIN CONDITIONS AND AS VEHICLES FOR ACTIVE INGREDIENTS

FIELD OF THE INVENTION

The present invention relates to aqueous compositions containing mixtures of synthetic polymers and biopolymers, useful in the treatment of skin and mucosal tissues dryness, and suitable as vehicles of active ingredients.

PRIOR ART DISCLOSURE

Skin and mucosal tissues dryness and dehydration are very frequent conditions and may be caused by environmental factors, viruses, bacteria, or associated with etiologically different primary diseases. When affecting mucous membranes, said conditions are usually described as dryness of the buccal cavity (e.g. dry stomatopharyngitis in Sj ögren's syndrome), of the vaginal, nasal and intestinal mucous membranes, and dryness of the eye (e.g. keratitis sicca).

Skin dryness and/or dehydration are not only important from an aesthetic point of view, but above all said conditions represent alterations of the cutis physiological function as a protective and defensive barrier. Furthermore, said dryness, which is per se a tissual damage causing lesions in the most serious cases, is also a hindrance to the absorption of possible products and/or drugs that can be administered in the treatment of the diseases affecting said tissues.

The methods most commonly used in the restoration of adequate moisture levels and in the prevention of further dehydration of the tissues consist in the application of creams, lotions or gels, which are capable of supplementing the water content of the tissues with highly hydrophilic agents or capable of forming a hydrophobic impermeable barrier on the tissue to be treated.

In the former case, it is well known in the state of the art the use of small synthetic hydrophilic molecules having humectant properties, such as glycerol, optionally mixed with water; it is also well known the use of macromolecules physiologically present in the tissues such as mucropolysaccharides, i.e. hyaluronic acid, dermatan sulfate and chondroitin sulfate, proteins such as collagen, elastin and placental proteins, having good properties as moisturizers and humectants.

As regards percutaneous absorption of active principles, it is to be stressed that the biological response to an active ingredient is often influenced by factors unrelated to the administered amount of the same principle. In particular, this is typical of topical administrations designed for local effect "in situ" as well as of oral administrations designed for absorption by general routes, which is often incomplete or in any case variable. In fact it is known that the bioavailability of active principles may be limited by the residence and contact times with the surface where absorption has to occur, e.g. the gastrointestinal tract in the case of oral preparations.

Therefore, several research works have lately been oriented to the development of bio- and/or mucoadhesive matrixes capable of binding themselves both to the stratum corneum of the cutis and to the film covering the mucous membranes, in particular the nasal one of the upper respiratory tract, the buccal, rectal, vaginal and ophthalmic ones.

The term "bioadhesion" has traditionally been used to describe the aggregation of biological and non-biological materials, rather than the interaction between materials having both biological origin. When the mucous membrane is covered by mucus, it is necessary to introduce the concept of mucoadhesion, which means that it is the same layer of mucus that comes into close contact with the adhesive substance through a typical "interface" phenomenon involving the interpenetration of the two phases.

Therefore, the "efficiency" of a bioadhesive matrix is influenced by specific physical and thermodynamic parameters, which determine the adhesion strength, and in particular by:

i) the "adhesive" molecular weight (e.g. the polyethylene glycol adhesiveness seems to increase with increasing the molecular weight, up to an optimal value of 4,000,000);

ii) the molecular mobility, which favors diffusion, and a sufficiently high viscosity;

iii) the ability to swell and form gels by osmosis with the substrate;

iv) the presence of functional groups capable of forming hydrogen bonds, such as carboxyl, hydroxyl, amido and sulphate groups.

However, the single parameters, though often related to the bioadhesive properties, are a necessary but not a sufficient condition for an adequate bioadhesive behaviour.

Among the substances having physicochemical properties predisposing to good bioadhesion and/or mucoadhesion, there are the aforesaid polysaccharides of biological derivation from mammalian tissues (hyaluronic acid, dermatan sulfate and chondroitin sulfate) as well as the polysaccharides of vegetable derivation, mostly from algae, such as alginic acid, gellan and other related mucropolysaccharides.

Other polysaccharides and cellulose and derivatives thereof (alkyl and carboxyalkyl), chitosan and chitin.

In addition to such polymers, synthetic polymers belonging to the families of polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol and Carbopol are also to be mentioned. An examplary highly hydrophilic and highly bioadhesive polymer is Carbopol Ex-55®, denominated Polycarbophil.

The bioadhesive behaviour of some compounds may be studied by in vitro, in vivo and ex vivo specific methods allowing qualitative and quantitative determinations (H. E. Junginger, *Pharm. Inc.*, 53, 11, 1056–1065, 1991).

Measurements made by said methods showed that Polycarbophil, the polymer mentioned above, has excellent adhesion strength and mucoadhesive properties, which were evaluated to be higher than 200% referred to the properties of pectin, which reference value was assumed 100%, sodium alginate was found to have satisfactory adhesion strength and mucoadhesive properties, evaluated at 126% approx.; instead, the mucoadhesion strength of polyvinyl alcohol was found to be 94.8% (H. E. Junginger, ibid, 1991).

The studies made in order to evaluate the ability of mucoadhesive polymers to act as vehicles of drugs and to release same at a controlled rate showed that some solutions containing Carbopol 934® slow the ileocecal transit (D. Harris et al., *J. of Controlled Release,* 12, 55–56, 1990), while Polycarbophil increases the intestinal absorption of peptidergic drugs (C. M. Lehr et al., *J. Phar. Pharmacol.,* 44, 402–407, 1992), polyvinyl alcohol increases the topical bioavailability of miconazole (M. F. Saettone et al., *J. of Controlled Release,* 16, 197–202, 1991) and sodium hyaluronate significantly increases the bioavailability of pilo-

carpine (M. F. Saettone, *Int. J. of Pharmaceutics,* 72, 131–139, 1991).

SUMMARY OF THE INVENTION

The Applicant has found aqueous compositions containing mixtures of synthetic polymers and biopolymers at different percent ratios; said mixtures unexceptedly exhibit higher bioadhesive properties than those of the polymers that are now recognized to have said properties to an optimal degree, such as Polycarbophil.

Said mixtures essentially consist of synthetic polymers, such as Polycarbophil and polyvinyl alcohol, associated with biopolymers, such as hyaluronic acid, alginic acid or dermatan sulfate, in the acidic form or in the form of salts thereof, in varying proportions.

The viscous behaviour of said compositions is characterized by particular physicochemical properties that substantially differentiate same from aqueous compositions containing only bioadhesive synthetic polymers; it follows that the topical application of the compositions of the invention is particularly advantageous. Said advantages arise from the bioadhesive and, in particular, the viscoelastic characteristics, as well as from the film-forming properties of said compositions.

It is a further object of the present invention the use of said compositions in the rehydration of skin or mucous membranes and/or as vehicles of active principles by topical application on said tissues.

It is a further object of the present invention to provide new compounds, i.e. dermatan sulfate and hyaluronic acid zinc salts, dermatan sulfate tetrabutylammonium salt, and mixed salts of dermatan sulfate or of hyaluronic acid with biotin and ethylenediamine, or with traumatic acid and ethylenediamine.

BRIEF DESCRIPTION OF THE DRAWINGS

The rheological properties and viscoelastic behaviour of the compositions according to the present invention will be better understood by reference to the enclosed drawings, wherein:

FIGS. 1*a* to 7*a* illustrate the flow curves (rheograms) relating respectively to samples B, A, D, H, I, C and G;

FIGS. 1*b* to 7*b* illustrate the oscillatory measurements relating respectively to samples B, A, D, H, I, C and G.

DETAILED DESCRIPTION OF THE INVENTION

The characteristics and advantages of the compositions according to the present invention will be better illustrated in the following detailed description.

The synthetic polymers used in the compositions of the present invention are selected from the group consisting of polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol and derivatives thereof, Carbopol and derivatives thereof; and preferably said synthetic polymers are polyvinyl alcohol or Polycarbophil.

Polyvinyl alcohol is a polymer having formula $(\text{—CH}_2\text{—CHOH—})_n$, prepared by alcoholysis of polyvinyl acetate.

The polymer found in commerce is characterized by different degrees of acetylation, which determine different physicochemical properties. Depending on the degree of polymerization, it may be soluble in aqueous solutions giving colloidal solutions, or in mixtures of water and alcohol.

This polymer is widely used in the industry of plastics and textiles as a non-ionic surfactant. In the pharmaceutical industry, it is amply used in the ophthalmic field to prepare useful solutions per se, e.g. artifical tears, or as a vehicle of ophthalmic drugs. It is also used in dermatology and for the cosmetic treatment of the skin (Martindale, *Extra Pharmacopeia,* 29th Ed., Pharmaceutical Press, 1989).

The other preferred synthetic polymer is Polycarbophil, a polyacrylic acid cross-linked with divinyl glycol (3,4-dihydroxy-1,5-hexadiene). The main characteristic of this polymer is a high water absorbing power; due to said physicochemical property, it is used in the form of calcium salt as a cathartic (Martindale, *Extra Pharmacopeia,* 29th Ed., Pharmaceutical Press, 1989). The use of said polymer as moisturizer and humectant is disclosed in European patent application No. 0 429 156 A1 and as a bioadhesive vehicle for the controlled release of active principles, in the pharmaceutical field, in U.S. Pat. No. 4,615,697.

The biopolymers used can be obtained from mammalian tissues, such as hyaluronic acid, dermatan sulfate and chondroitin sulfate, which play a key role in differentiation, growth and migration of cells, as well as in extracellular matrix organization; or they can be obtained from vegetables, such as alginic acid. Said polysaccharides are characterized by specific and distinctive functional groups, but they all show a high molecular weight and a marked hydrophilic power.

In particular, alginic acid, a polyuronic acid extracted from algae and composed of mannuronic and L-guluronic acid residues, is amply used in the food industry as thickener and in the pharmaceutical industry as antiacid and, in the form of calcium salt, as haemostatic. Hyaluronic acid and dermatan sulfate, deriving on the opposite from animal tissues, are characterized the former by glucuronic acid and glucosamine, and the latter by iduronic acid and sulphate groups.

Among the above mentioned biopolymers, hyaluronic acid has been particularly studied concerning both its biological role and the pharmacological or cosmetic properties. Recent studies have shown that hyaluronic acid is the most specific ligand of CD44 receptor, a protein localized on cell surface. It is to be noted that CD44 is also able to bind, with a lower affinity, chondroitin-4-sulfate and chondroitin-6-sulfate (Aruffo et al. "CD44 is the principal cell surface receptor for hyaluronate". *Cell,* 61: 1303–1313, 1990). To further specify such a functional interaction, it has been shown that CD44 receptor and hyaluronic acid are co-distributed in epithelia having similar functional program, i.e. keratinizing oral epithelium, hair follicle and nail cells (C. Wang et al. "Distribution of hylauronan and its CD44 receptor in the epithelia of human skin appendages", *Histochemistry,* 98: 105–112, 1992). According to these evidences, hyaluronic acid has found extensive pharmaceutical applications in the osteoarticular, ophthalmic and dermatologic fields and for the cosmetic treatment of the skin. Also its homologue chondroitin sulfate is widely used in the pharmaceutical field as an anti-hyperlipoproteinaemic agent in atherosclerosis and as artifical tears in the form of eyewash.

High molecular weight dermatan sulfate is used because of its anticoagulant properties, analogous to those of heparin. However, said properties are not observed in the low molecular weight polymer (F. Dol et al., *J. Lab. Clin. Med.,* 115, 1, 43–51, 1990).

Moreover, it is noteworthy the fact that the presence in the bioadhesive and mucoadhesive compositions of the inven-

tion of biopolymers able to bind, through a well defined epitope, to a specific receptor, such as hyaluronan and CD44, leads to a preferential distribution via receptor-binding of the biopolymers themselves, as well as the active principles optionally delivered.

All the above biopolymers are usually used in the form of sodium salt; however, in the preparation of the aforesaid bioadhesive compositions, they can be used also in the form of other commonly available salts, such as salts of alkali or alkaline-earth metals and ammonic salts.

Furthermore, said biopolymers can be used in the form of new salts, such as lithium and zinc salts, or mixed salts with a diaminic compound, such as ethylenediamine or piperazine, and a biocompatible compound having a carboxylic group, such as biotin or traumatic acid, which form a further object of the present invention. More specifically, salification is carried out by bridging the carboxylic groups of the byopolimer and of said biocompatible compound by means of a suitable organic compound carrying at least two aminic groups, such as for example ethylenediamine or piperazine, or carrying at least two quaternary ammonic substituents. Said mixed salts of biopolymers, according to the present invention, are preferably the salt with biotin and ethylenediamine, and the salt with traumatic acid and ethylenediamine, particularly suitable for supplying oligo-elements or vitamins to the tissue (skin or mucous membranes) treated with the compositions of the invention.

The methods for the preparation of the above mentioned salts may vary depending on the polysaccharide nature and physico-chemical characteristics. In fact, some polysaccharides are water-soluble both in the acidic and salified forms (Methods 1 and 2), while some others are poorly water-soluble in the acidic form and soluble in the form of salts (Methods 3 and 4). Finally, other polysaccharides are soluble in the acidic form and water-insoluble in the form of salts (Methods 5 and 6).

We report hereinafter suitable methods of preparation of the aforesaid salts, corresponding to the above cases; some of the them are already known in the state of the art, while others, even if new, are easily deducible by the men skilled in the art.

Said methods allow the obtainment of salts of mono and bivalent ions, as well as of higher-valence ions, which can salify the carboxylic groups of the polysaccharide; moreover, according to the reported preparation procedures, it is possible to obtain salts of the aforesaid biopolymers with primary, secondary or tertiary organic amines, or with quaternary ammonic compounds.

Furthermore, said methods may be conveniently used to obtain the mixed salts of said biopolymers with diaminic compounds and biocompatible compounds having a carboxylic group.

Method I

A quantity of salified polysaccharide in the most currently available form, generally the sodium salt, partially salified to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is eluted in a column cooled to 4° C., containing a slight excess of a cationic exchange resin such as 50×8 Dowex®, generated in H^+ form. The sodium-free eluate is collected under continued stirring in a solution cooled to 4° C. and containing an equivalent amount of the counterion with which the polysaccharide is to be salified, properly prepared in the free base form. The obtained product may be collected by precipitation in a non-solvent or by drying processes operating under mild conditions, such as lyophilization or spray-drying.

Method II

A quantity of salified polysaccharide in the most currently available form, generally the sodium salt, partially salified to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is dialyzed at 4° C. vs. an aqueous solution of a salt (MX) of the cation with which the polymer is to be salified until the dialyzate is sodium-free and then vs. distilled water to remove excess MX, if any. The obtained product may be collected by precipitation in a non-solvent or by drying processes operating under mild conditions, such as lyophilization or spray-drying.

Method III

A quantity of salified polysaccharide in the most currently available form, generally the sodium salt, partially salified to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is eluted in a column cooled to 4° C., containing a slight excess of a cationic exchange resin such as 50×8 Dowex®, generated in the ionic form of the counterion with which polymer is to be salified. The product contained in the eluate may be collected by precipitation in a non-solvent or by drying processes operating under mild conditions, such as lyophilization or spray-drying.

Method IV

A quantity of salified polysaccharide in the most currently available form, generally the sodium salt, partially salified to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is slowly added with an equivalent amount of mineral acid, under continued stirring, at 4° C. The polysaccharide that precipitates in the acidic form is separated by filtration, washed and suspended again in distilled water at 4° C. An equivalent amount of the counterion with which the polymer is to be salified, properly prepared in the free base form is added to the polymer suspension in the acidic form. The soluble salt obtained by salification may be collected by precipitation in a non-solvent or by drying processes operating under mild conditions, such as lyophilization or spray-drying.

Method V

A quantity of polysaccharide partially salified with an alkaline earth metal (Ca^{++} or Ba^{++}) to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is added slowly and under continued stirring with an equivalent amount of a suitable salt of the counterion with which the polymer is to be salified, properly salified with an anion bringing about the formation of a precipitate with the alkaline earth metal; the formation of insoluble calcium or barium sulphate will be particularly convenient. The precipitate is separated by filtration and discarded, while the product contained in the solution may be collected by precipitation in a non-solvent or by drying processes operating under mild conditions, such as lyophilization or spray-drying.

Method VI

A quantity of salified polysaccharide in the most currently available soluble form, generally the sodium salt, partially salified to obtain 1.0 equivalent of free anionic functional groups (carboxyls and/or sulphates), is solubilized in distilled water. The solution is added slowly and under continued stirring with an equivalent solution of a convenient salt of the cation with which the polymer is to be salified, preferably a halide, sulphate, nitrate or acetate of said cation. The precipitate is separated by filtration, washed and dried under vacuum, while the solution is discarded.

We report hereinbelow for illustrative but not limitative purposes the following examples describing the preparation of the new hyaluronic acid and dermatan sulfate salts of the present invention, according to the general methods described above.

EXAMPLE 1

Preparation of dermatan sulfate lithium salt

Dermatan sulfate sodium salt (25.2 g), having an average molecular weight of 5,000 to 8,000 daltons, was solubilized in distilled water (200 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in Li^+ form. The sodium-free eluate was frozen and lyophilized to give 23.3 g of product.

The physicochemical properties of the dermatan sulfate lithium salt are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{14}H_{19}NO_{14}SLi_2$
molecular weight	471.26 (disaccharide unit)
elemental analysis	
theoretical:	C = 35.68%; H = 4.06%; N = 2.97%; O = 47.53%; S = 6.80%; Li = 2.95%
experimental:	C = 35.55%; H = 4.10%; N = 2.92%; O = 47.70%; S = 6.68%; Li = 2.90%
water solubility	>10 mg/ml

EXAMPLE 2

Preparation of dermatan sulfate zinc salt

Dermatan sulfate sodium salt (25.2 g), having an average molecular weight of 5,000 to 8,000 daltons, was solubilized in distilled water (200 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in Zn^{++} form. The sodium-free eluate was frozen and lyophilized to give 26.05 g of product.

The physicochemical properties of the dermatan sulfate zinc salt are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{14}H_{19}NO_{14}SZn$
molecular weight	522.74 (disaccharide unit)
elemental analysis	
theoretical:	C = 32.17%; H = 3.66%; N = 2.68%; O = 42.85%; S = 6.13%; Zn = 12.51%
experimental:	C = 32.05%; H = 3.72%; N = 2.63%; O = 42.92%; S = 6.15%; Zn = 12.48%
water solubility	>10 mg/ml

EXAMPLE 3

Preparation of hyaluronic acid zinc salt

Hyaluronic acid sodium salt (40.1 g), having an average molecular weight of 1,000,000 daltons, was solubilized in distilled water (8,000 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in Zn^{++} form. The sodium-free eluate was frozen and lyophilized to give 40.8 g of product.

The physicochemical properties of the hyaluronic acid zinc salt are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{14}H_{20}N_{11}Zn_{1/2}$
molecular weight	411.0 (disaccharide unit)
elemental analysis	
theoretical:	C = 40.91%; H = 4.90%; N = 3.41%; O = 42.82%; Zn = 7.95%
experimental:	C = 40.80%; H = 4.97%; N = 3.38%; O = 43.00%; Zn = 7.81%
water solubility	>5 mg/ml

EXAMPLE 4

Preparation of dermatan sulfate mixed salt with biotin and ethylenediamine

Dermatan sulfate sodium salt (50.3 g), having an average molecular weight of 5,000 to 8,000 daltons, was solubilized in distilled water (500 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (240 ml), generated in H^+ form. The sodium-free eluate was collected under continued stirring in a solution cooled to 4° C., containing biotin (48.8 g) and ethylenediamine (12.0 g). The resulting solution was frozen and lyophilized to give 106.2 g of product.

The physicochemical properties of the low molecular weight dermatan sulfate mixed salt with biotin and ethylenediamine are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{38}H_{69}N_9O_{20}S_3$
molecular weight	1068.19 (disaccharide unit)
elemental analysis	
theoretical:	C = 42.73%; H = 6.51%; N = 11.80%; O = 29.96%; S = 9.00%
experimental:	C = 42.65%; H = 6.60%; N = 11.64%; O = 29.74%; S = 6.25%
biotin	45.74% (w/w)
water solubility	>10 mg/ml

EXAMPLE 5

Preparation of dermatan sulfate mixed salt with traumatic acid and ethylenediamine

Dermatan sulfate sodium salt (50.3 g), having an average molecular weight of 5,000 to 8,000 daltons, was solubilized in distilled water (500 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (240 ml), generated in H^+ form. The sodium-free eluate was collected under continued stirring in a solution cooled to 4° C., containing traumatic acid (22.8 g) and ethylenediamine (12.0 g). The resulting solution was frozen and lyophilized to give 80.3 g of product.

The physicochemical properties of the low molecular weight dermatan sulfate mixed salt with traumatic acid and ethylenediamine are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{30}H_{57}N_5O_{18}S$
molecular weight	807.86 (disaccharide unit)
elemental analysis	
theoretical	C = 44.60%; H = 7.11%; N = 8.67%; O = 35.65%; S = 3.97%
experimental:	C = 44.65%; H = 7.16%; N = 8.54%; O = 35.72%; S = 3.91
traumatic acid	28.26% (w/w)
water solubility	>10 mg/ml

EXAMPLE 6

Preparation of hyaluronic acid mixed salt with biotin and ethylenediamine

Hyaluronic acid sodium salt (40.1 g), having an average molecular weight of 1,000,000 daltons, was solubilized in distilled water (8,000 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in H^+ form. The sodium-free eluate was collected under continued stirring in a solution cooled to 4° C., containing biotin (24.4 g) and ethylenediamine (6.0 g). The resulting solution was frozen and lyophilized to give 67.9 g of product.

The physicochemical properties of the high molecular weight hyaluronic acid mixed salt with biotin and ethylenediamine are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{20}H_{45}N_5O_{14}S$
molecular weight	683.73 (disaccharide unit)
elemental analysis	
theoretical:	C = 45.67%; H = 6.63%; N = 10.24%; O = 32.67%; S = 4.69%
experimental:	C = 45.24%; H = 6.85%; N = 10.18%; O = 33.12%; S = 4.61%
biotin	35.73% (w/w)
water solubility	>10 mg/ml

EXAMPLE 7

Preparation of hyaluronic acid mixed salt with traumatic acid and ethylenediamine

Hyaluronic acid sodium salt (40.1 g), having an average molecular weight of 1,000,000 daltons, was solubilized in distilled water (8,000 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in H^+ form. The sodium-free eluate was collected under continued stirring in a solution cooled to 4° C., containing traumatic acid (11.4 g) and ethylenediamine (6.0 g). The resulting solution was frozen and lyophilized to give 67.9 g of product.

The physicochemical properties of the high molecular weight hyaluronic acid mixed salt with traumatic acid and ethylenediamine are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{22}H_{39}N_3O_{13}$
molecular weight	553.56 (disaccharide unit)
elemental analysis	
theoretical:	C = 47.74%; H = 7.10%; N = 7.59%; O = 37.57%
experimental:	C = 47.34%; H = 7.18%; N = 7.46%; O = 38.02%
traumatic acid	20.62% (w/w)
water solubility	>10 mg/ml

EXAMPLE 8

Preparation of dermatan sulfate tetrabutylammonium salt

Dermatan sulfate sodium salt (25.2 g), having an average molecular weight of 5,000 to 8,000 daltons, was solubilized in distilled water (200 ml). The solution was eluted in a column cooled to 4° C., containing the cationic exchange resin 50×8 Dowex® (120 ml), generated in the tetrabutylammonium form. The sodium-free eluate was frozen and lyophilized to give 47.0 g of product.

The physicochemical properties of the dermatan sulfate tetrabutylammonium salt are as follows:

physical state	whitish amorphous powder
empirical formula	$C_{46}H_{93}N_3O_{14}S$
molecular weight	944.33 (disaccharide unit)
elemental analysis	
theoretical:	C = 58.51%; H = 9.93%; N = 4.45%; O = 23.72%; S = 3.40%
experimental:	C = 58.23%; N = 10.01%; N = 4.51%; O = 23.78%; S = 3.47%
water solubility	>10 mg/ml

The bioadhesive and mucoadhesive compositions according to the present invention contain synthetic and biological polymers preferably at the following concentrations: polyvinyl alcohol, at a concentration ranging from 0.1 to 4% by wt., Polycarbophil at a concentration ranging from 0.1 to 2% by wt., hyaluronic acid having an average molecular weight of 800,000 to 1,200,000 daltons or salts thereof at a concentration ranging from 0.05% to 5% by wt., low and medium viscosity alginic acid or salts thereof at a concentration ranging from 0.5% to 5% by wt., dermatan sulfate having average molecular weight of 5,000 to 8,000 daltons and salts thereof at a concentration ranging from 0.05% to 5% by wt.

The bioadhesive and viscoelastic aqueous compositions of the invention may consist of binary, ternary or quaternary associations of said synthetic and biological polymers, depending on the requirements as well as on the desired degree of bioadhesion and/or physicochemical and rheological properties.

Due to their physicochemical properties, such bioadhesive compositions adhere to mammalian skin and mucous membranes, moisturizing and protecting same from irritative agents. Furthermore, they may usefully be employed in the administration of active principles: in fact, compared with non-bioadhesive matrixes, they improve bioavailability of active principles by prolonging the contact time with the skin or mucosa. In fact, bio- and mucoadhesive bases are active "in loco" for approx. 10–20 hours, i.e. for the period equivalent to the time of turnover of the strata cornea of the epidermis or of mucin. Therefore, a prolonged contact time results in an improved absorption of the active principle.

Furthermore, compared with the compositions known in the state of the art, the claimed compositions, which contain both biopolymers and synthetic polymers, offer the advantage of a higher biocompatibility with the contacted tissues, when applied to the site where they have to exert their action.

Therefore, the bioadhesive compositions according to the present invention are suitable for the prevention and treatment of conditions characterized by excessive skin and mucous membranes dryness (of the mouth, nose, upper respiratory tract, gastrointestinal tract, eye and vagina), even when induced by irritants and physiopathologic causes. Furthermore, being primarily capable of correcting the skin and mucous membranes alterations caused by dehydration, the bioadhesive compositions of the invention also act as vehicles of active principles, whereby the active principles bioavailability is improved, the residence time "in situ" prolonged and/or the absorption improved.

The bioadhesive compositions according to the present invention are prepared by a method consisting of sequential steps. It is described herein by way of example, for illustrative but not limitative purposes, the preparation of a composition containing two synthetic polymers (Polycarbophil and polyvinyl alcohol), a biopolymer (hyaluronic acid) and triethanolamine as salifying agent of the polymers and as thickener.

EXAMPLE 9

Preparation of the compositions of the invention

1) A planetary turboemulsifier of stainless steel provided with paddles counterrotating at variable speed and with heating/cooling jacket was fed, under constant agitation, in the order with demineralized water (50% by wt. of the total) and Polycarbophil. The turboemulsifier was worked under vacuum at −76 mmHg, for at least 15 min.

Once turboemulsifying had been completed, the mass was maintained under stirring at high shear rates until perfect homogenization.

2) At the same time, a melter of stainless steel, equipped with heating jacket and counterrotating paddles, was fed in the order with demineralized water (35.55% by wt. of the total) and polyvinyl alcohol. The melter was heated to 85±2° C. At that temperature, the mass was maintained under mixing until a perfectly clear solution was obtained.

3) Once the two aforesaid steps had been completed, the mass contained in the melter was added slowly, under continuous stirring and in a thin stream, to the mass contained in the planetary turboemulsifier, whose inside was maintained under constant vacuum. The resulting mass was maintained under continuous stirring until a completely homogeneous phase was obtained. The resulting mass was cooled under vacuum to 30±2° C. At that temperature, the mass was maintained under stirring and in vacuo.

4) Solution A was separately prepared in a suitable vessel of stainless steel, provided with agitator, by addition in the order of demineralized water (10% by wt. of total) and of a biopolymer, e.g. hyaluronic acid. Agitation was continued until a viscous, perfectly homogeneous and clear solution was obtained.

5) Solution A was added slowly and in a thin stream to the mass contained in the turboemulsifier, under continuous stirring and under constant vacuum at −76 mmHg. Agitation was continued until a perfectly homogeneous mass was obtained.

A gel of the desired density may be obtained by adding for example triethanolamine and operating according to the following steps, subsequent to step 5);

6) Solution B consisting of demineralized water (1% by wt. of the total) and triethanolamine was prepared instantly in a suitable vessel of stainless steel.

7) Solution B was added under continuous stirring to the mass contained in the turboemulsifier. Agitation was continued until complete carbomers swelling and a perfectly homogeneous gel were obtained. Once the mass had gelled completely, mixing was stopped and the pressure inside the turboemulsifier was slowly restored. The gelled mass was then discharged into containers of stainless steel.

For illustrative but not limitative purposes, the physicochemical properties of the compositions according to the present invention, obtained by the aforesaid method, are herein reported in Table 1. Concentrations are by weight: balance to 100 is water.

TABLE 1

Physiochemical properties of bioadhesive formulations

Bioadhesive comp.	Conc. %	pH	Viscosity	Density	Ref.
Polycarbophil	1.00	5.2 ± 0.5	3,100	1.0050	C
Polyvinyl alcohol	1.50				
Hyaluronic acid	0.15				
Polycarbophil	0.20	5.3 ± 0.5	230	1.0020	D
Polyvinyl alcohol	0.30				
Hyaluronic acid	0.15				

TABLE 1-continued

Physiochemical properties of bioadhesive formulations

Bioadhesive comp.	Conc. %	pH	Viscosity	Density	Ref.
Polycarbophil	1.00	6.8 ± 0.5	2,700	1.0100	E
Polyvinyl alcohol	1.50				
Sodium Alginate	1.00				
Polycarbophil	1.00	6.5 ± 0.5	6,000	1.0200	F
Polyvinyl alcohol	1.50				
Sodium Alginate	2.00				
Polycarbophil	1.00	6.6 ± 0.5	10,000	1.0250	G
Polyvinyl alcohol	1.50				
Sodium Alginate	3.00				
Polycarbophil	0.20	5.2 ± 0.5	400	1.0050	H
Polyvinyl alcohol	1.50				
Hyaluronic acid	0.30				
Polycarbophil	0.20	5.2 ± 0.5	50	1.0050	I
Polyvinyl alcohol	1.50				
Dermatan sulfate	0.15				

Viscosity, expressed as centipoises (cp) at 20° C., was measured with a viscometer CONTRAVES ® TVB.
Density (relative 20/20° C.) was measured with a picnometer for semifluids vs. the density of water.

Measurement of bioadhesive properties

In order to check the bioadhesive properties, the adhesion strength of the aforesaid compositions (marked C to I) was evaluated in comparison with mucin, Carbopol 940® and the bioadhesive polymer Polycarbophil at a concentration of 1% by wt. (composition A) and of 0.20% by wt. (composition B) in water, i.e. at the concentrations at which said polymer exhibited the best mucoadhesive properties (Junginger, op. cit., 1991).

In particular, the adhesion work, i.e. the force of adhesion (separation) by elongation of the mucin surfaces, was measured. The tests were carried out according to the methods described in literature (Saettone et al., Int.J.Pharm., 51, 203–212, 1989), in the absence of dipping solution.

The formulation under examination (75 μl) was stratified on the upper support provided with a centrally pierced ring nut limiting the surface (inside diameter of 1.20 cm). The measurement (platform fall rate 2.50 mm/min) was made after 1 min of contact between the surfaces.

The data obtained by recording the force (F) required for separating the two surfaces (formulation and mucous layer), as a function of the elongation (l) of same, were processed by a computer. The area under the curve obtained (AUC), representing the adhesion work (L) (F,l), was thus calculated.

Table 2 shows the values and the average values ±S.E. (expressed as erg/cm2) of the AUCs of the compositions under investigation as well as the average values of a reference formulation (polyacrylic acid [Carbopol 940®]. 2.5% neutralized gel) and of mucin (swine gastric mucin [Tokyo Kasei Kogyo, Japan], 25.0% dispersion).

TABLE 2

AUC values of bioadhesive matrices.											
comp. n°	A	B	C	D	E	F	G	H	I	C940 ®	Mucin
1	457.08	381.11	608.13	398.91	497.01	803.46	742.69	474.00	524.36		
2	361.15	339.88	601.62	485.29	637.65	666.30	861.40	554.74	483.99		
3	375.47	438.41	539.98	499.18	760.06	579.92	923.26	619.85	402.82		
4	374.60	411.06	462.72	408.89	539.98	576.44	793.04	520.45	489.19		
5	441.45		460.11	405.85	553.00		993.58	428.86	380.68		
6							827.55	574.27			
average	401.95	392.61	534.51	439.62	597.54	656.53	856.92	528.69	456.21	304.23	118.20
S.E.	19.64	21.12	32.13	21.65	46.60	53.20	37.00	28.34	27.44	26.63	9.00

The experimental results prove that Polycarbophil has excellent bioadhesiveness and adhesion strength and that there is no significant difference between the bioadhesive properties of Polycarbophil at a concentration of 1% by wt. (A) and at a concentration of 0.2% by wt. (B). The mucoadhesion strength of all tested formulations (C to I) is much higher than that of mucin and of C940®, and even of Polycarbophil (A and B), which suggests that the association of biopolymers at different concentrations can improve the adhesion strength and therefore mucoadhesive properties.

Measurements of rheological properties

In order to check whether said compositions, besides exhibiting improved bioadhesive properties, also had significant rheological properties, viscosity measurements, flow curves and oscillatory measurements were carried out to evaluate the viscoelastic behaviour.

Viscosity measurements and flow curves

The samples (A,B,C,D,G,H, and I) were analyzed with a viscometer HAAKE® RS100, with flat-cone measurement systems C35/4° at 23° C., and compared within the same range of applied stress (0–50 Pa). Flow curves (rheograms) were recorded (FIGS. 1*a* to 7*a*): the conical rotor was subjected to a shear rate and, at the same time, stress τ and viscosity η were recorded. Table 3 shows the viscosity values obtained at a constant shear rate $\dot{\gamma}$. A shear rate of 50 sec^{-1} was chosen for low viscosity samples and a shear rate of 0.5 sec^{-1} for high viscosity samples.

Sample B (0.2% Polycarbophil) was found to be a "stiff gel", the elastic modulus (G')/viscous modulus (G") ratio being high. The values of said elastic modulus (G') and viscous modulus (G") are constant and parallel with varying rotor angular speed, which further indicates a "stiff gel" structure. A probable creep limit is observed (FIG. 1*b*).

Sample A (1% Polycarbophil) shows an analogous behaviour, but the non-linear, i.e. slightly curvilinear, trend of the δ-Cor angle (displacement angle between vectors G' and G") with varying rotor angular speed indicates a lower stability of the gel, while probable fracture effects appear in its structure (FIG. 2*b*).

That is the intrinsic behaviour of Polycarbophil; instead, when it is mixed with other polymers, the gel is destructured: the creep limit value decreases until disappearing when passing from B (FIG. 1*b*) to D (FIG. 3*b*). Among the investigated compositions containing 0.2% Polycarbophil, sample H exhibits the highest viscosity. Furthermore, its viscoelastic behaviour is particularly interesting, since the elastic modulus increases more markedly than the viscous modulus, which indicates that sample H tends to change from stiff gel to viscous polymer. Said behaviour seems to be due to the presence of hyaluronic acid and to result from the average molecular weight and from the molecular weight distribution of the polymers in solution (FIG. 4*b*).

Sample I, which is characterized by the presence of low molecular weight dermatan sulfate, has lower viscosity than sample H, associated with the lower average molecular weight of the polysaccharide. In any case, said sample exhibits an interesting behaviour, analogous to that of newtonian liquids, the trend of the stress τ/shear rate $\dot{\gamma}$ ratio being almost linear (FIGS. 5*a*, *b*).

Sample C, compared with sample A, appears as a polymer solution rather than a stiff gel, which indicates that the physicochemical properties of the polysaccharide hyaluronic acid prevail over those of Polycarbophil (FIG. 6*b*).

TABLE 3

Viscosity η of bioadhesive matrices									
Comp. Ref.	A	B	C	D	E	F	G	H	I
η/50 S^{-1} (Pa · s)		0.800		0.400				0.550	0.220
η/0.5 S^{-1} (Pa · s)	100		100		—	—	73		

Viscosity η was measured in Pascal.sec (Pa · s).

Oscillatory measurements

The samples (A,B,C,D,G,H, and I) were analyzed with a viscometer HAAKE® RS100, with flat-cone measurement system C35/4° at 23° C., with oscillation frequency varying from 0.0464 to 4.64 Hz and an applied stress of 0.50 Pa for samples B, D, H and I and of 4.00 Pa for samples A, C and G.

The oscillatory measurements, made to distinguish the "viscous" from the "elastic" character of the formulations, gave the results shown in FIG. 1*b* to 7*b*.

Sample G is substantially a very viscous polymer solution. The curve representing the viscous modulus intersects the curve representing the elastic modulus at high angular speed values, which suggest the presence of a high average molecular weight polymer and a good molecular weight distribution (FIG. 7*b*).

It may be noted that the association of synthetic polymers, such as Polycarbophil and polyvinyl alcohol, with biopolymers, such as alginic acid, hyaluronic acid and dermatan sulfate, yields compositions with a marked bioadhesive behaviour and with the viscous character prevailing over the elastic one. This is an undoubted advantage, the "adhesiveness" being a property more closely related to the viscous modulus than to the elastic one and being the basis of the film-forming ability of said compositions.

In fact, if the "still gel" type rheological behaviour of Polycarbophil is modified by adding the aforesaid compositions with a viscous component, said compositions show not only improved adhesive properties but above all an improved film-forming ability. Thanks to their improved bioadhesiveness and viscosity, the compositions of the invention can provide stable film on the tissue to be treated, securing a better contact surface between the compositions and the same tissue and, consequently, a more adequate protection and/or moisturizing.

According to the aforesaid experimental results, the compositions of the invention have higher bioadhesive and, in particular, mucoadhesive properties than Polycarbophil, which is to date regarded as the molecule with the best bioadhesive properties, utilized in various formulations suitable for moisturizing mucous membranes and for releasing drugs at a controlled rate after oral or topical administration.

The bioadhesive compositions of the invention, formulated as hydrogels and/or viscous solutions with varying rheological consistency (from semisolid to apparently liquid) depending on the intended applications, are therefore meant to treat pathological conditions or even less severe alterations associated with the so-called paraphysiological situations in the following districts:

Cutaneous:

a) due to their moisturizing properties, useful in dryness/dehydration conditions caused by environmental factors or deriving from particular pharmacological treatments (e.g. keratolytic) or secondary to other diseases, e.g. eczema and dermatitis, or in situations for which tissue moisturizing is very important, e.g. decubitus ulcers:

b) due to their bioadhesive properties, in association with antimycotics, steroid and non-steroid anti-inflammatory agents or antibacterial agents for treating mycosis, burns and ulcers of different nature.

Ophthalmic:

a) as moisturizers/humectants in the treatment of disorders such as keratitis sicca or neuroparalytica, or of diseases simply caused by atmospheric factors or by foreign bodies fitting over the cornea, such as contact lenses;

b) as mucoadhesive matrix capable of increasing the contact time of specific drugs contained therein, necessary for the pathology under treatment.

The intraocular concentration of a drug is partly determined by the rate of its elimination from the conjunctival and episcleral circle. In fact, the typical vasodilatation of the eye involves a faster outflow of the active principle administered: it is, therefore, very important to prolong the contact time between the drug and the corneal epithelium. In particular, said drugs may be for example anti-inflammatory agents, anti-histamines for treating external eye diseases of allergic origin, antimycotics for treating keratites, specific antibiotics for treating viral infections, or antiglaucomatous or vasoactive agents.

Buccal:

a) in the form of mouthwash or gel, due to their moisturizing characteristics for treating xerostomia, both caused by irradiating treatments and associated with Sjögren's syndrome, senility or administration of drugs, such as tricyclic antidepressants;

b) in the form of a specific mouthwash, gel or paste, associated with oral cavity disinfectants for daily hygiene, for treating infections, or associated with antimycotics/antibiotics and anti-inflammatory agents for treating diseases such as for example candidiasis, muguet, stomatomucositis, paradontopathy, dental plaque and dismicrobism.

Tracheobronchial;

a) in the form of vaporization, due to their moisturizing and humectant characteristics, for treating dryness;

b) associated with antibiotics/antibacterial agents and/or anti-inflammatory agents for treating the inflammation of the upper respiratory tract.

Vaginal:

a) in the form of gynaecologic wash, due to their humectant characteristics, for treating vaginites of various nature, accompanied by mucosal dryness;

b) as a matrix capable of releasing drugs at a controlled rate, in particular in association with specific antimycotics, antibacterial or anti-inflammatory agents.

Gastroenteric and rectal:

a) due to their mucoadhesive and film-forming properties, for treating diarrhoea and consequent dehydration, and due to their ability to gel when coming into contact with water;

b) as a drug-delivery system, associated with drugs that would be insufficiently or variably absorbed by other administration routes or requiring a hepatic by-pass.

We report hereinbelow for illustrative but not limitative purposes the following examples of the pharmaceutical compositions according to the present invention, useful per se for the treatment of dryness conditions in the aforesaid districts.

EXAMPLE 10

Ophthalmic fluid gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Polycarbophil	0.20
Hyaluronic acid	0.15
Thimerosal	0.01
Sodium chloride	0.65
Disodium hydrogen phosphate.12 H_2O	0.30
Sodium dihydrogen phosphate.2 H_2O	0.03
Demineralized water	q.s. to 100

EXAMPLE 11

Eyewash (by wt. % composition)	
Polyvinyl alcohol	0.15
Polycarbophil	0.20
Hyaluronic acid	0.15
Thimerosal	0.01
Sodium chloride	0.65
Disodium hydrogen phosphate.12 H_2O	0.30
Sodium dihydrogen phosphate.2 H_2O	0.03
Demineralized water	q.s. to 100

EXAMPLE 12

Eyewash (by wt. % composition)	
Polycarbophil	0.20
Dermatan sulfate	0.30
Thimerosal	0.01
Sodium chloride	0.65
Disodium hydrogen phosphate.12 H_2O	0.30

-continued

Sodium dihydrogen phosphate.2 H_2O	0.03
Demineralized water	q.s. to 100
EXAMPLE 13	
Gynaecologic gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Triethanolamine	1.50
Polycarbophil	1.00
Sodium alginate	1.00
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100
EXAMPLE 14	
Dermatologic gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Triethanolamine	1.50
Polycarbophil	1.00
Sodium alginate	2.00
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100
EXAMPLE 15	
Dental gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Triethanolamine	1.50
Polycarbophil	1.00
Sodium alginate	3.00
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100

The compositions of the present invention may also be used as vehicles of active principles useful for the treatment of cutis and mucous membranes diseases. We report hereinbelow for illustrative but not limitative purposes the following examples.

EXAMPLE 16	
Gynaecologic gel (by wt. % composition)	
2-Phenylphenol	0.30
Methyl p-hydroxybenzoate	0.10
Ethyl p-hydroxybenzoate	0.10
*Eumulgin HRE 40 ®	1.00
Triethanolamine	0.20
Polycarbophil	1.00
Polyvinyl alcohol	1.50
Hyaluronic acid	0.10
Vitamin A Palmitate 2,000 IU/g	0.20
Hyaluronic acid salt (Ex. 7)	0.06
Chondroitin 6-sulfate	0.20
Demineralized water	q.s. to 100
*Eumulgin HRE 40 ® : polyoxyethylenated castor oil	
EXAMPLE 17	
Dermatologic gel (by wt. % composition)	
2-Phenylphenol	0.30
Methyl p-hydroxybenzoate	0.10
Ethyl p-hydroxybenzoate	0.10
Eumulgin HRE 40 ®	1.00
Triethanolamine	0.275
Polycarbophil	1.00
Polyvinyl alcohol	1.00
Hyaluronic acid	0.15
Vitamin A Palmitate 2,000 IU/g	0.20
Hyaluronic acid salt (Ex. 6)	0.06
Dodecenedioic acid	0.05
Demineralized water	q.s. to 100
EXAMPLE 18	
Gynaecologic solution (by wt. % composition)	

-continued

2-Phenylphenol	0.30
Methyl p-hydroxybenzoate	0.10
Ethyl p-hydroxybenzoate	0.10
Eumulgin HRE 40 ®	1.00
Hydroxyethylcellulose	0.50
Lactic acid (80%)	2.00
Triethanolamine	2.30
Polycarbophil	0.20
Polyvinyl alcohol	0.30
Hyaluronic acid	0.15
Vitamin A Palmitate 2,000 IU/g	0.20
Hyaluronic acid salt (Ex. 3)	0.20
Demineralized water	q.s. to 100
EXAMPLE 19	
Dermatologic gel (by wt. % composition)	
2-Phenylphenol	0.30
Methyl p-hydroxybenzoate	0.10
Ethyl p-hydroxybenzoate	0.10
Eumulgin HRE 40 ®	1.00
Polycarbophil	1.00
Polyvinyl alcohol	1.50
Dermatan sulfate	0.15
Vitamin A Palmitate 2,000 IU/g	0.20
Quercetin	0.01
Dermatan sulfate salt (Ex. 4)	0.06
Triethanolamine	0.25
Chondriotin 6-sulfate	0.20
Demineralized water	q.s. to 100
EXAMPLE 20	
Gynaecologic gel (by wt. % composition)	
Glycerin	10.00
Eumulgin HRE 40 ®	2.00
Polycarbophil	1.00
Hyaluronic acid	0.30
Triethanolamine	0.25
Vitamin A Palmitate 2,000 IU/g	0.20
Methyl p-hydroxybenzoate	0.10
Ethyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.15
Methyl Paraben	0.10
Dodecenedioic acid, cetrimide salt	0.05
N-(2-hydroxyethyl)-hexadecanamide	0.01
Demineralized water	q.s. to 100
EXAMPLE 21	
Eyewash (by wt. % composition)	
Polycarbophil	0.20
Dermatan sulfate salt (Ex. 5)	0.30
Thimerosal	0.01
Sodium chloride	0.65
Disodium hydrogen phosphate.12 H_2O	0.30
Sodium hydrogen phosphate.2 H_2O	0.03
Demineralized water	q.s. to 100
EXAMPLE 22	
Dental gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Triethanolamine	1.50
Polycarbophil	1.00
Dermatan sulfate salt (Ex. 8)	3.00
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100
EXAMPLE 23	
Dermatologic gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Triethanolamine	1.50
Polycarbophil	1.00
Dermatan sulfate (Ex. 2)	2.00
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100
EXAMPLE 24	
Gynaecologic gel (by wt. % composition)	

-continued

Polyvinyl alcohol	0.20
Polycarbophil	1.00
Hyaluronic acid	0.10
N,N'-bis-(2-hydroxyethyl)-nonandiamide	0.20
Glycerin	10.00
Propylene glycol	1.00
Hydrogenated castor oil (40)OE*	1.00
Tocopheryl acetate	0.50
Phenylethyl alcohol	0.15
Methyl p-hydroxybenzoate	0.10
Quercitin	0.01
Sodium hydroxide (30% by wt. solution)	0.20
Demineralized water	q.s. to 100

*Hydrogenated castor oil (40)OE is polyoxyethylenated with 40 moles ethylene oxide/mole.

EXAMPLE 25

Dental gel (by wt. % composition)	
Polyvinyl alcohol	1.50
Polycarbophil	1.00
Sodium alginate	3.00
N,N'-bis-(2-hydroxyethyl)-nonandiamide	0.20
Triethanolamine	1.50
Methyl p-hydroxybenzoate	0.10
2-Phenylethanol	0.10
Ethyl p-hydroxybenzoate	0.10
Demineralized water	q.s. to 100

EXAMPLE 26

Dental gel (by wt. % composition)	
Polyvinyl alcohol	0.200
Polycarbophil	0.200
Hyaluronic acid	0.050
N,N'-bis-(2-hydroxyethyl)-nonandiamide	1.000
Trans-2-dodecendioic acid	0.005
Xylitol	7.500
Carboxymethylcellulose sodium salt	4.500
Hydrogenated castor oil (40)OE*	0.500
2,4-Dichlorobenzylic alcohol	0.150
Cytromint	0.150
Colour CI 42090	0.025
Colour CI 19140	0.015
Demineralized water	q.s. to 100

*Hydrogenated castor oil (40)OE is polyoxyethylenated with 40 moles ethylene oxide/mole.

EXAMPLE 27

Dental mouthwash (by wt. % composition)	
Polycarbophil	0.100
Hyaluronic acid	0.0500
PTC*	57.1429
N,N'-bis-(2-hydroxyethyl)-nonandiamide	0.0100
Trans-2-dodecendioic acid	0.005
Xylitol	7.5000
Polysorbate 20	1.0000
2,4-Dichlorobenzylic alcohol	0.1500
Cytromint	0.1000
Colour CI 42090	0.1000
Demineralized water	q.s. to 100

*PTC (Polyphenolic Tea Complex) indicates an aqueous extract containing 0.15–0.4% by weight of D(*)-catechin, obtained by treating 1 kg of green tea (leaves) in demineralized water (20–30 1), at a temperature of 60–80° C., for a period of 10–30 minutes.

EXAMPLE 28

Dental spray (by wt. % composition)	
Polyvinyl alcohol	0.200
Hyaluronic acid	0.050
N,N'-bis-(2-hydroxyethyl)-nonandiamide	1.000
Trans-2-dodecendioic acid	0.005
Xylitol	7.500
Hydrogenated castor oil (40)OE*	0.500
Cytrimint	0.180
2,4-Dicholorobenzylic alcohol	0.150
Demineralized water	q.s. to 100

*Hydrogenated castor oil (40)OE is polyoxyethylenated with 40 moles ethylene oxide/mole.

We claim:

1. A highly bioadhesive and mucoadhesive aqueous composition useful in the rehydration of the skin and mucosal tissues and/or as a vehicle for active principles in percutaneous absorption, comprising:
   (a) polycarbophil in an amount ranging from about 0.1 to 2% by wt;
   (b) polyvinyl alcohol in an amount ranging from about 0.1 to 4% by weight; and
   (c) a biopolymer selected from the group consisting of:
      (1) hyaluronic acid and salts thereof, in an amount ranging from about 0.05% to 5% by weight, said hyaluronic acid having an average molecular weight ranging from about 800,000 to 1,200,000 daltons,
      (2) dermatan sulfate and salts thereof, in an amount ranging from about 0.05% to 5% by weight, said dermatan sulfate having an average molecular weight of about 5,000 to 8,000 daltons;
      (3) chondroitin sulfate, and salts thereof; and
      (4) alginic acid and salts thereof in an amount ranging from about 0.5% to 5% by weight.

2. The aqueous composition according to claim 1, characterized in that said hyaluronic acid salts are selected from the group consisting of zinc salt, mixed salt with biotin and ethylenediamine, and mixed salt with traumatic acid and ethylenediamine.

3. The aqueous composition according to claim 1, characterized in that said dermatan sulfate salts are selected from the group consisting of lithium, zinc and tetrabutylammonium salts, mixed salt with biotin and ethylenediamine, and mixed salt with traumatic acid and ethylenediamine.

4. The aqueous composition according to claim 1, characterized in that said active to be vehiculated in percutaneous absorption is selected from the group consisting of antimycotics, steroid and non-steroid anti-inflammatory agents, antibacterial agents, anti-histamines, antibiotics, antiglaucomatous agents, vasoactive agents and disinfectants.

5. A process for the preparation of a bioadhesive and mucoadhesive aqueous composition of claim 1 comprising the following steps:
   (a) complete homogenization of said polycarbophil and polyvinyl alcohol in water, wherein homogenization is carried out in a single pot, or in two separate pots with subsequent combination of the resulting masses under continuous stirring;
   (b) preparation of a homogeneous solution of one of said biopolymers in water; and
   (c) adding of the solution obtained in (b) to the mixture obtained in (a), under continuous stirring, until complete homogenization of a mass is obtained.

6. The process according to claim 5, where a water solution of a thickening agent is added under stirring to the mass obtained in step (c).

7. The process according to claim 6, characterized in that said thickening agent is triethanolamine.

8. A method for treating skin and mucosa tissues to dryness and dehydration, which comprises administration of a bioadhesive and mucoadhesive aqueous composition as defined in claim 1.

9. The aqueous composition according to claim 1, characterized in that said mucosal tissues are selected from the group consisting of cutaneous, ophthalmic, buccal, tracheobronchial, vaginal, gastroenteric and rectal tissues.

10. A vehicle comprising active principles for percutaneous absorption in a bioadhesive and mucoadhesive aqueous composition as defined in claim 1.

11. A dermatan sulfate salt selected from the group consisting of mixed salt with biotin and ethylenediamine, and mixed salt with traumatic acid and ethylenediamine.

12. The salt according to claim 11, characterized in that said dermatan sulfate has an average molecular weight ranging from 5,000 to 8,000 daltons.

13. A hyaluronic acid salt selected from the group consisting of mixed salt with biotin and ethylenediamine and mixed salt with traumatic acid and ethylenediamine.

14. The salt according to claim 13, characterized in that said hyaluronic acid has an average molecular weight ranging from about 800,000 to 1,200,000 daltons.

15. The aqueous composition according to claim 1, wherein said polycarbophil is a polyacrylic acid cross-linked with divinylglycol.

* * * * *

US006174524B1

(12) United States Patent
Bawa et al.

(10) Patent No.: **US 6,174,524 B1**
(45) Date of Patent: **Jan. 16, 2001**

(54) **GELLING OPHTHALMIC COMPOSITIONS CONTAINING XANTHAN GUM**

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(73) Assignee: **Alcon Laboratories, Inc.**, Fort Worth, TX (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/277,102**

(22) Filed: **Mar. 26, 1999**

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(51) **Int. Cl.**[7] **A61K 31/74**

(52) **U.S. Cl.** **424/78.04**; 514/912

(58) **Field of Search** 424/78.04; 514/912

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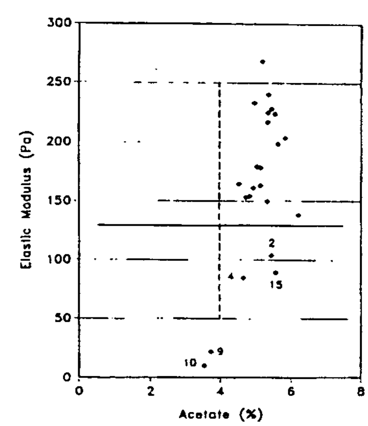
(74) *Attorney, Agent, or Firm*—Patrick M. Ryan

(57) **ABSTRACT**

Ophthalmic drug delivery vehicles which are administrable as a liquid and which gel upon contact with the eyes are disclosed. The vehicles contain xanthan gum.

13 Claims, 4 Drawing Sheets



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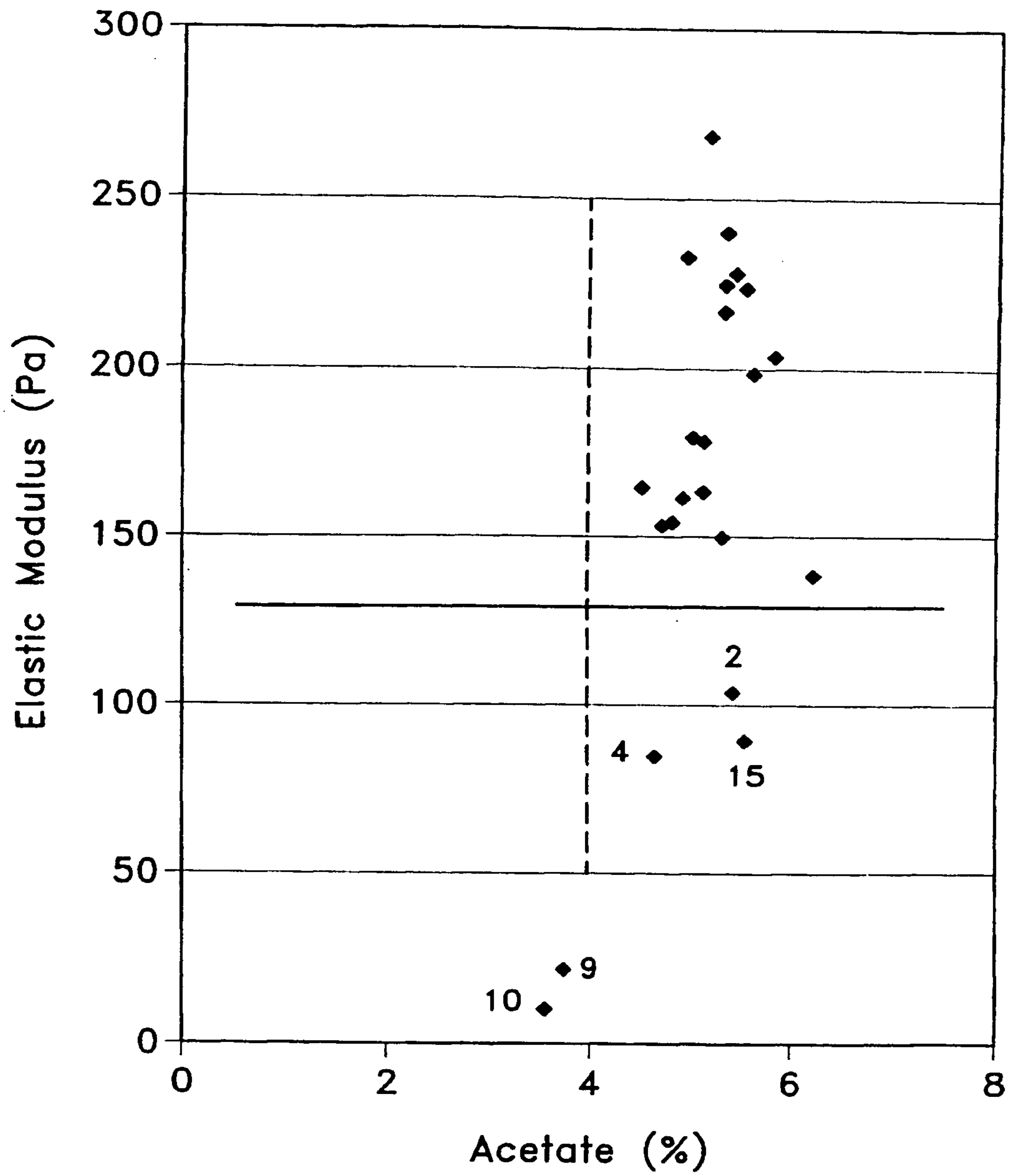
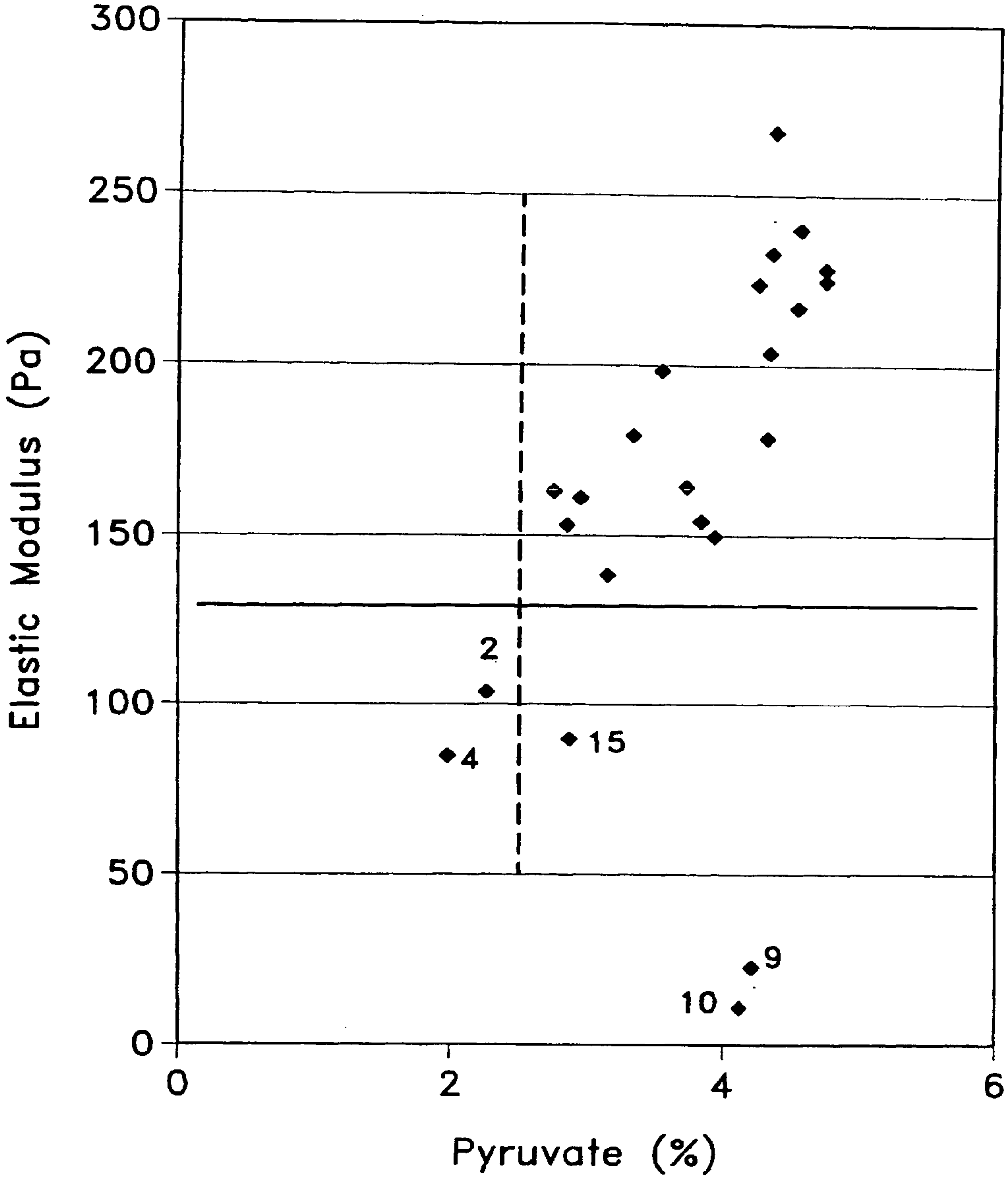

300
250
200
150
100
50
0
Elastic Modulus (Pa)
0
2
4
6
8
Acetate (%)
2
4
15
9
10

FIG. 1



300
250
200
150
100
50
0
Elastic Modulus (Pa)
0
2
4
6
Pyruvate (%)
2
4
15
9
10

FIG. 2

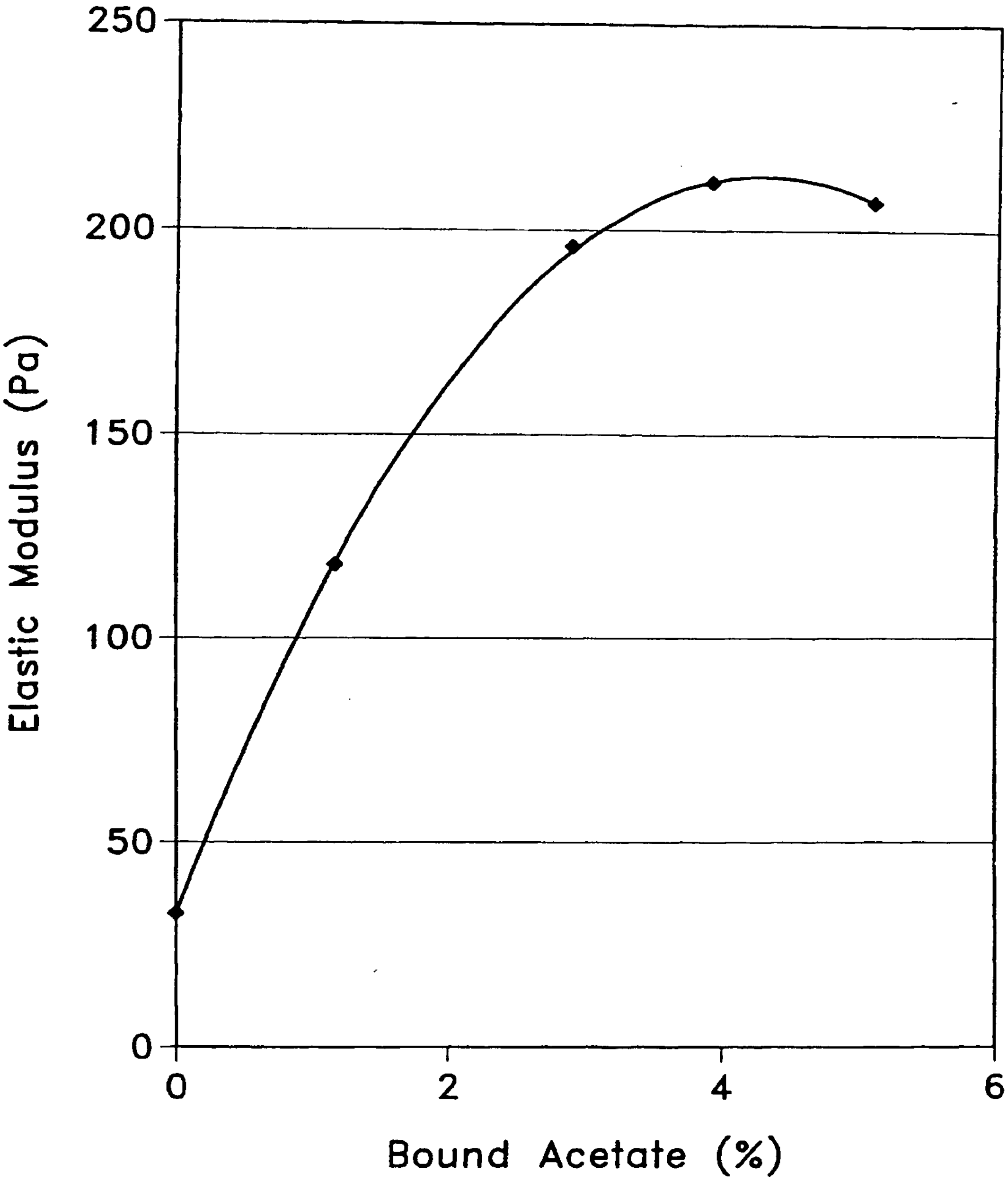


FIG. 3

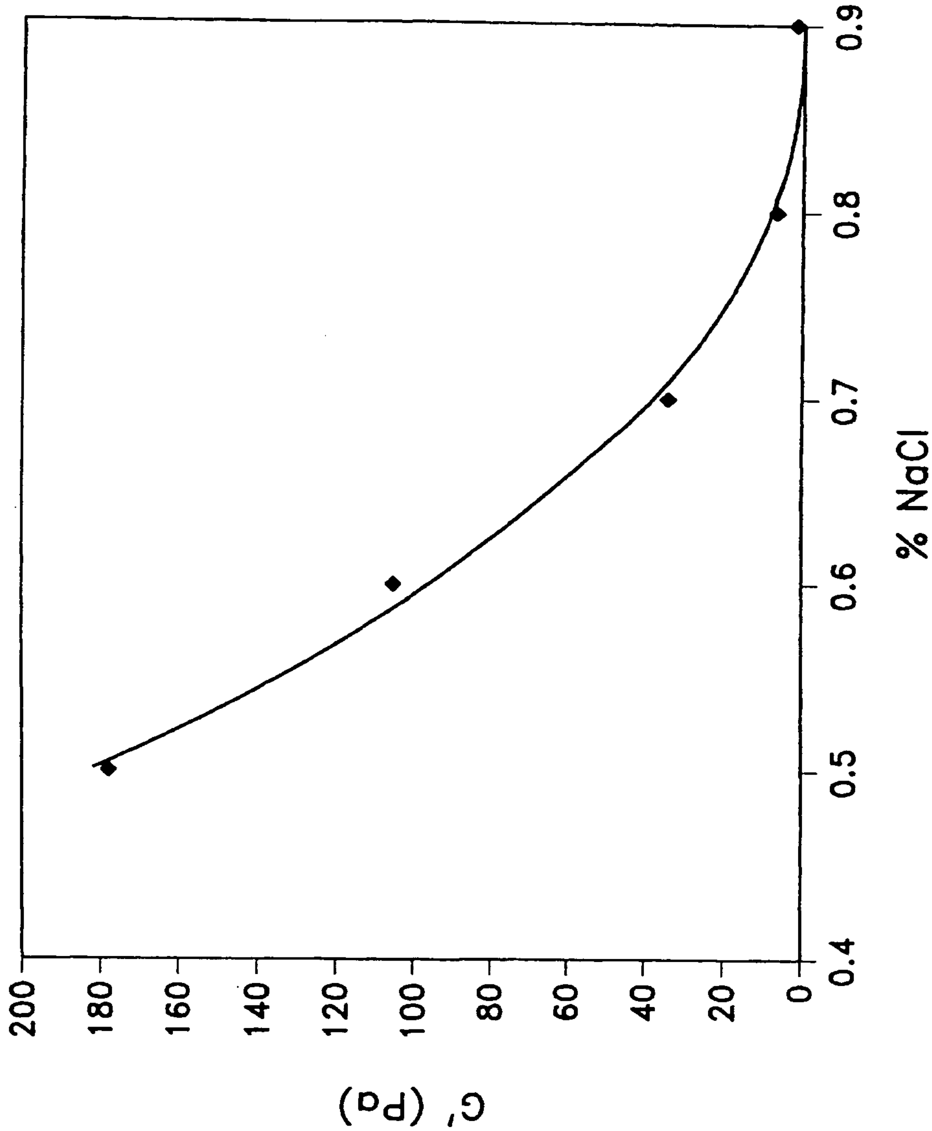


FIG. 4

GELLING OPHTHALMIC COMPOSITIONS CONTAINING XANTHAN GUM

This application claims priority to co-pending U.S. Provisional Application, U.S. Ser. No. 60/081,004, filed Apr. 7, 1998.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to pharmaceutical compositions. In particular, this invention relates to ophthalmic compositions and drug delivery vehicles which are administrable as liquids and which gel upon contact with the eye.

2. Description of Related Art

Although gels are desirable because they prolong the contact or residence time of drugs in the eye, they are not as easy to administer topically as liquid drops. A variety of gelling drug delivery systems have been developed in an effort to allow an ophthalmic pharmaceutical composition to be topically administered as a liquid drop and then gel upon contact with the eye. Drug delivery vehicles containing polysaccharide polymers which gel in response to a pH change have been proposed, such as those described in U.S. Pat. Nos. 4,136,173, 4,136,177, and 4,136,178, for example.

Drug delivery systems which gel in response to temperature changes have also been proposed. For example, drug delivery systems utilizing Tetronic®, Pluronic®, or other polyols have been disclosed in U.S. Pat. Nos. 4,474,751; 4,474,752; and 4,188,373. U.S. Pat. Nos. 5,124,151; 5,306,501 and 5,618,800 also disclose thermally gelling systems.

Alternatively, ion-sensitive gelling polymers have been identified. European Patent No. 0 227 494 B1 discloses ophthalmic compositions containing polysaccharides of the type that undergo liquid-gel phase transition under the effect of an increase in ionic strength. The only representative polysaccharide specifically disclosed by this European patent, however, is gellan gum. U.S. Pat. No. 5,403,841 discloses gelling ophthalmic compositions that contain carrageenans, such as *Eucheuma Carrageenani*. The carrageenan-containing compositions are characterized as capable of gelling in about 0.5 to 1% aqueous NaCl.

International Publication No. WO 92/09307 discloses gelable carrier compositions containing a water-soluble, nonionic cellulose ether polysaccharide, such as ethylhydroxyethylcellulose, and a charged surfactant. The reference compositions gel due to strong hydrophobic interactions between the polymer and the charged surfactant.

Various drug delivery systems employing combinations of two types of gelling polymers have also been disclosed. U.S. Pat. No. 5,077,033 discloses a thermally irreversible gel system comprising a combination of polyoxyalkylene and ionic polysaccharides. U.S. Pat. No. 5,296,228 discloses aqueous reversibly gelling polymeric solutions containing ion exchange resin particles. The polymeric component of the solution may be a pH sensitive polymer, a temperature sensitive polymer, or combinations of both pH-sensitive polymers and temperature sensitive polymers. U.S. Pat. No. 5,252,318 also discloses reversibly gelling aqueous compositions containing combinations of polymers, in this case at least one pH-sensitive reversibly gelling polymer and at least one temperature sensitive reversibly gelling polymer.

U.S. Pat. No. 5,212,162 discloses ophthalmic compositions containing gelling polysaccharides and drug carrier substrates. As used in the '162 patent, gelling polysaccharide means a polysaccharide capable of reversible liquid-to-gel transition based on a change in ionic strength or pH. According to the '162 patent, suitable gelling polysaccharides include xanthan gum, locust bean gum, gellan gum, carrageenans and combinations thereof. The '162 patent references U.S. Pat. Nos. 4,136,173, 4,136,177, and 4,136,178 in connection with xanthan gum and locust bean gum.

EP 0 424 043 A1 discloses liquid ophthalmic compositions that undergo liquid-gel phase transition upon administration to the eye. The compositions comprise an aqueous solution of at least one active agent and are characterized in that they contain 0.1 to 5% by weight of a sulfated polysaccharide derivative, preferably selected from kappa-carrageenan, iota-carrageenan and mixtures thereof, whereby the liquid-gel phase transition is mediated by interaction of the sulfated polysaccharide derivative with the proteins of the lachrymal fluid.

Xanthan gum is a polysaccharide known to be useful in ophthalmic compositions as a viscosity enhancing agent. U.S. Pat. No. 4,136,177 discloses ophthalmic compositions containing an ophthalmic drug and from about 0.01 to 2.5% (w/v) of xanthan gum. The '177 patent teaches that if the concentration of xanthan gum is from about 0.02 to about 1.0% (w/v), the composition is suitable for "dropwise" ophthalmic applications. In contrast, at concentrations of xanthan gum above about 1.0% and up to about 2.5% (w/v), "a gel-like consistency is attained." Thus, the '177 patent discloses compositions that are formulated to be either non-gelled liquids or gels before instillation in the eye. The '177 patent does not describe any xanthan gum-containing compositions as capable of being administered as a liquid and gelling upon contact with the eye.

U.S. Pat. No. 4,136,173 discloses ophthalmic compositions containing a combination of xanthan gum and locust bean gum. These compositions gel due to a change in pH. The '173 patent discloses that, in solutions containing either of these two gums alone, "sufficient gelling did not occur, nor, at the same time, did these solutions demonstrate pH sensitive liquid-gel reversibility." ('173 patent, Col. 4, lines 1–4).

It has been accepted in the art that xanthan gum is not a polymer of the type which is capable of undergoing a liquid-gel phase transition upon contact with the eye. See, for example, Meseguer, et al., Journal of Ocular Pharmacology and Therapeutics, 12(4):481–487 (1996), describing gellan gum as a "phase-transition system" but xanthan gum as a "viscosity enhancer."

SUMMARY OF THE INVENTION

The present invention is directed toward ophthalmic compositions which are administrable as a liquid and which gel upon contact with the eye. The compositions of the present invention contain xanthan gum, but do not contain locust bean gum.

Among other factors, the present invention is based upon the finding that compositions containing xanthan gum as the sole gelling polymer are capable of gelling upon contact with the eye.

Among other factors, the present invention is based upon the finding that xanthan gum gels upon contact with the eye due, at least in part, to an interaction with the lysozyme component of tear fluid.

Among other factors, the present invention is also based upon the finding that the strength of the gel formed by xanthan gum upon contact with lysozyme is dependent upon both the acetate and pyruvate content of xanthan gum.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the relationship between elastic modulus (G', Pa) and acetate content for xanthan gum.

FIG. 2 shows the relationship between elastic modulus (G', Pa) and pyruvate content for xanthan gum.

FIG. 3 shows the relationship between elastic modulus (G', Pa) and bound acetate content for xanthan gum.

FIG. 4 shows the relationship between elastic modulus (G', Pa) and NaCl concentration.

DETAILED DESCRIPTION OF THE INVENTION

The ophthalmic compositions of the present invention are formulated as non-gelled liquids which gel upon instillation in the eye. The compositions contain xanthan gum as a gelling agent, and do not contain locust bean gum. Xanthan gum is a well-known polysaccharide that is commercially available from a variety of sources. The amount of xanthan gum contained in the compositions of the present invention will depend upon the identity and concentration of other ingredients in the composition, but will generally range from about 0.1 to about 1% (w/w).

It is important that the xanthan gum contained in the compositions of the present invention have an initial bound acetate content of at least about 4%. Bound acetate content means the amount of acetate esterified to the xanthan gum molecule (w/w). Bound acetate content can be measured by HPLC methods and may be available from the commercial suppliers of xanthan gum.

It is also important that the xanthan gum have an initial bound pyruvate concentration of at least about 2.5%. The bound pyruvate content means the amount of pyruvate which is bound to the xanthan gum molecule in a ketal form (w/w). The bound pyruvate content can be measured by calorimetric or HPLC methods and is commonly available from the commercial suppliers of xanthan gum.

As used herein, "initial" bound acetate or pyruvate content of xanthan gum means that content present in the raw material as received from the supplier, measured before the expiration date assigned to the raw material by the supplier and prior to any processing or formulating.

The ability of xanthan to form a gel upon contact with the eye can be affected both by the identity and amount of other ingredients in the compositions of the present invention and by subsequent processing steps, such as a steam sterilization step. Once formulated and processed to finished form, the ability of the xanthan gum-containing compositions of the present invention to gel upon contact with the eye may change over time as well, due in part to changes in the bound acetate content over time. By restricting the initial bound acetate and pyruvate content as described above, the xanthan gum raw material to be included in the compositions of the present invention is selected based on its ability to form relatively strong gels—on the order of approximately 130 Pa (elastic modulus, G')-5 when measured using the Lysozyme Gel Strength Test described in Example 1 below.

Ophthalmic drugs suitable for use in the compositions of the present invention include, but are not limited to: anti-glaucoma agents, such as beta-blockers including timolol, betaxolol, levobetaxolol, carteolol, miotics including pilocarpine, carbonic anhydrase inhibitors, prostaglandins, seretonergics, muscarinics, dopaminergic agonists, adrenergic agonists including apraclonidine and brimonidine; anti-infective agents including quinolones such as ciprofloxacin, and aminoglycosides such as tobramycin and gentamicin; non-steroidal and steroidal anti-inflammatory agents, such as suprofen, diclofenac, ketorolac, rimexolone and tetrahydrocortisol; growth factors, such as EGF; immunosuppressant agents; and anti-allergic agents including olopatadine.

The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt, such as timolol maleate, brimonidine tartrate or sodium diclofenac. Compositions of the present invention may also include combinations of ophthalmic drugs, such as combinations of (i) a beta-blocker selected from the group consisting of betaxolol and timolol, and (ii) a prostaglandin selected from the group consisting of latanoprost; 15-keto latanoprost; fluprostenol isopropyl ester (especially 1R-[1α(Z),2β(1E,3R*),3α,5α]-7-[3,5-dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)-phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester); and isopropyl [2R(1E,3R),3S(4Z),4R]-7-[tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate.

Although the amount of drug included in the compositions of the present invention will be whatever amount is therapeutically effective and will depend upon a number of factors, including the identity and potency of the chosen drug, the total concentration of drug will generally be about 5% (w/w) or less. Alternatively, the compositions of the present invention may be formulated without ophthalmic drugs, in which case the compositions may serve in the prevention or treatment of dry eye.

In addition to xanthan gum and any ophthalmic drug, the compositions of the present invention may include other components. For example, the compositions may include one or more pharmaceutically acceptable buffering agents, preservatives (including preservative adjuncts), tonicity-adjusting agents, surfactants, solubilizing agents, stabilizing agents, comfort-enhancing agents, emollients, pH-adjusting agents and/or lubricants. The compositions of the present invention may also contain drug carrier substrates, such as cation exchange resins, anion exchange resins, encapsulating microspheres, insoluble drug particles, gel particles and polymeric drug complexes.

As mentioned above, the identity and amount of additional ingredients in the xanthan gum compositions of the present invention can effect the compositions' 15 ability to gel upon contact with the eye. In this regard, the compositions of the present invention should be formulated so that their total ionic strength is approximately 120 mM or less, and preferably about 94 mM or less. Compositions containing xanthan gum that have a total ionic strength greater than about 120 mM are unlikely to gel upon contact with the eye. Total ionic strength is calculated according to the well accepted formula: Ionic strength=$0.5\Sigma m_i Z_i^2$, where m_i is the molar concentration of ionized specie i with a valency of Z_i. As used herein, "total ionic strength" excludes any contribution from xanthan gum itself.

Xanthan gum is generally available in at least two grades from some commercial suppliers, a food or industrial grade and a pharmaceutical grade. It is preferable to polish filter even pharmaceutical grade materials so that the finished pharmaceutical product will have increased clarity. As one skilled in the art appreciates, the appropriate filter size for polish filtration depends upon the size of the undesired impurities contained in raw material. For example, in the case of a solution composition, it has been found that the Rhodigel Clear grade of xanthan gum from Rhone- Poulenc Inc. should be filtered through a 0.45 μm filter in order to remove cell debris and impurities. Multiple stages of filters can be used to increase the overall efficiency of the polish filtration process.

If xanthan gum is to be sterilized using steam or heat, the length of time xanthan is exposed to elevated temperatures is preferably minimized. By using relatively higher target

temperatures and shorter residence times to achieve a desired sterilization, including relatively rapid ramp up and ramp down times, the effect of elevated temperatures upon xanthan gum's ability to gel can be reduced.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLES

Example 1

Measurement of Gel Strength of Xanthan Gum Raw Material Using Lysozyme ("the Lysozyme Gel Strength Test").

An in vitro test is used to measure the gel strength (elastic modulus, G') of xanthan gum raw material after mixing with lysozyme, a protein found in tears. While not wishing to be bound by any theory, it is believed that xanthan gum undergoes an ionic interaction with lysozyme to form a gel. The gel strength is measured as follows:

Prepare a 0.6% (w/w) aqueous solution of xanthan gum containing 0.5% (w/w) NaCl using purified water. Add 2.0 g of the aqueous solution of xanthan gum to 4.0 g of a freshly prepared 0.2% (w/w) solution of chicken lysozyme (chicken lysozyme in purified water) contained in a 20 mL scintillation vial. Immediately mix the resulting sample for 30 seconds on a wrist action shaker using the shaker parameters listed below (shaking is a critical step). Following shaking, allow the sample to stand for 3–4 minutes. Perform remaining steps as quickly as possible. Gently isolate the resulting gelatinous mass by pouring the contents of the scintillation vial onto a 180 mm nylon mesh filter and allow to drain for approximately 10 seconds. Gently slide the filtered sample onto the center of the stage of a Bohlin constant stress rheometer. Gently lower the upper plate of the rheometer to spread the sample over the entire bottom surface of the upper plate. Allow the sample to equilibrate for 4 minutes. Measure elasticity in the oscillation mode using the instrumental parameters shown below. Average the results for 3–8 replicate samples to obtain a final result.

Parameters for Wrist Action Shaker (Lab-Line 3589-1 or equivalent)	
Cycle (up & down) time	700–750 rpm
Vertical Displacement	10–12 mm
Arm Length	14–15 cm
Geometry	Clamp at 45° angle from vertical in a plane perpendicular to arm motion

Parameters for Bohlin Constant Stress Rheometer (Bohlin CS-10 or equivalent)	
Plate	40 mm parallel geometry, stainless steel
Gap	1.3 mm
Mode	Oscillation
Frequency	1 Hz
Shear Stress	0.25 Pa
Temperature	34° C.
Delay Time	5 seconds
Wait Time	10 seconds
Resolution	High

The gel strength of 23 different lots of xanthan gum obtained from various suppliers was tested using the Lysozyme Gel Strength Test, and gel strength (elastic modulus, G') results for each lot are listed in Table 1. These results are also shown in FIG. 1 (elastic modulus vs. acetate content) and FIG. 2 (elastic modulus vs. pyruvate content). Initial bound acetate and pyruvate content was measured using ion exclusion HPLC with ultraviolet detection (205 nm). Xanthan gum raw material was dissolved in purified water and analyzed for hydrolyzed ("free") acetate and pyruvate content. A separate solution of the same lot of xanthan gum was subjected to an acid hydrolysis step prior to HPLC analysis to determine total acetate and pyruvate content. Bound acetate and pyruvate are calculated by the differences between the total and free values.

TABLE 1

LOT #	INITIAL BOUND PYRUVATE (%)	INITIAL BOUND ACETATE (%)	ELASTIC MODULUS G' (Pa)
1	3.4	5.1	180
2	2.3	5.5	104
3	2.8	5.2	164
4	2	4.7	85
5	3	5	162
6	3.6	5.7	199
7	3.2	6.3	139
8	2.9	4.8	154
9	4.2	3.7	22
10	4.1	3.5	10
11	4	5.4	150
12	4.4	5.2	179
13	3.8	4.6	165
14	3.9	4.9	155
15*	2.9	5.6	90
16	4.3	5.6	224
17	4.6	5.4	217
18	4.4	5.9	204
19	4.4	5	233
20	4.6	5.4	240
21	4.8	5.5	228
22	4.8	5.4	225
23	4.4	5.2	268

*This sample was expired; it was >11 years old.

Example 2

Ophthalmic Compositions

The ophthalmic compositions shown below in Table 2 can be prepared according to the present invention. All values are expressed as % w/v unless otherwise noted.

TABLE 2

INGREDIENT	A	B	C (vehicle)
Timolol Maleate	0.34	0.68	—
Benzododecinium Bromide	0.012	0.012	0.012
Xanthan Gum	0.6	0.6	0.6
Tromethamine	0.72	0.8	0.6
Boric Acid	0.3	0.3	0.3
Mannitol	4.35	3.75	4.4
Polysorbate 80	0.05	0.05	0.05
Purified Water	q.s. 100	q.s. 100	q.s. 100
INGREDIENT	**D**	**E**	**F**
Xanthan Gum	0.3	0.3	0.3
HPMC*	—	—	0.25
Tromethamine	q.s. pH 6–8	q.s. pH 6–8	q.s. pH 6–8
Mannitol	q.s. 250–300 mOsm	q.s. 250–350 mOsm	q.s. 250–350 mOsm
Glycerin	—	0.2	—
Purified Water	q.s. 100	q.s. 100	q.s. 100
INGREDIENT	**G**	**H**	**I**
Xanthan Gum	0.6g	0.6 g	0.6g
Cartelol	—	1.05 g	2.1g
Mannitol	—	3.4 g	3 g
Sorbitol	4.5g	—	—
Boric Acid	0.3g	0.3 g	0.3 g
Tromethamine	0.7g	0.561	0.54 g

TABLE 2-continued

Polysorbate 80	0.05 g	0.05 g	0.05 g
Benzododecinium Bromide	0.012g	0.012g	0.012 g
Purified Water	qs to 100 g	qs to 100 g	qs to 100 g
pH	7.5	6.7	6.7

INGREDIENT	J (% w/w)
Polysorbate 80	0.05
Xanthan Gum	0.4–0.8
Mannitol	4.4
Boric Acid	0.3
Tromethamine	0.6
Benzalkonium Chloride	0.01 + 10% xs
Purified Water	

INGREDIENT	K
Olopatadine HCl	0.111
Xanthan Gum	0.6
Boric Acid	0.3
Mannitol	4.4
Tromethamine	0.64
Polysorbate 80	0.05
Benzalkonium Chloride	0.01
Tromethamine	q.s. pH 7
Hydrochloric Acid	q.s. pH 7
Purified Water	q.s. to 100

*HPMC = hydroxypropyl methylcellulose

Example 3

Effect of Acetate Content on Gel Strength

To demonstrate the effect of bound acetate content on the ability of xanthan gum to gel upon contact with lysozyme, xanthan gum having an initial bound acetate content of 5.2% was progressively deacylated as follows. A stock solution containing 0.75 wt % xanthan gum and 0.4625 wt % NaCl was prepared. To the 40.0 g of stock solution, the indicated amount of 1N NaOH was added. The solution was stirred for ten minutes at room temperature. Then the indicated amount of 1N HCl was added. The pH of the solution was adjusted to 7 with 0.1N NaOH. Then the indicated amount of sodium chloride was added, followed by purified water to adjust sample size to 50.0 g and stirring for one hour. Each of the five solutions had final concentrations of 0.6% xanthan gum and 0.5% NaCl. The results are shown below in Table 3 and in FIG. 3.

The NaCl concentration contributions from the stock solution and from NaOH/HCl are also shown below. The approximate weight of the NaCl contributed to the composition by NaOH/HCl was calculated as (MW_{NaCl} X weight of 1N NaOH added)/1000.

TABLE 3

	SAMPLE				
	A	B	C	D	E
0.75% xanthan gum, 0.46% NaCl stock, g	40	40	40	40	40
1N NaOH, g	0	0.11	0.2	0.5	1.1
1N HCl, g	0	0.11	0.2	0.5	1.1
NaCl, g	0.064	0.0576	0.0524	0.0349	0
Purified Water, g	q.s. 50	q.s. 50	q.s. 50	q.s. 50	q.s.50
% NaCl from Stock	0.37	0.37	0.37	0.37	0.37
% NaCl from NaOH & HCl*	0	0.01287	0.0234	0.0585	0.1287
% NaCl added to sample after HCl	0.128	0.1152	0.1048	0.0698	0
% Total NaCl	0.498	0.49807	0.4982	0.4983	0.4987
Osmolality, mOsm	181	182	182	183	188
Free Pyruvate	None@	None@	None@	None@	None@
Free Acetate, % of xanthan wt.	0	1.2	2.2	3.9	5.2
Gel Strength (G', Pa) (individual)	207	223	181	97	38
	195	232	81*	59*	41
	189	224	194	128	28
	235	168	214	134	28
Gel Strength (G', Pa) (Average)	207	212	196	120	34

*Not considered for calculation of average because it is 3 standard deviations away from the average of the remaining three readings.
@Below detection limit.

Example 4

Effect of Other Composition Ingredients and Xanthan Gum Concentration on Gel Strength

To demonstrate the effect of composition ingredients and xanthan gum concentration on gel strength, the formulations shown below were prepared and tested using the Lysozyme Gel Strength Test. The results are shown in Table 4 (all amounts are expressed in % w/w).

TABLE 4

	SAMPLE								
INGREDIENT	A	B	C	D	E	F	G	H	I
Betaxolol HCl	—	0.28	—	—	—	—	—	—	—
(S)-Betaxolol HCl	0.168		0.28	0.4	0.56	0.84	0.75	0.84	0.84
Xanthan Gum	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	1
Amberlite IRP-69	—	0.25	0.25	0.45	0.65	1.5	2.5	1.125	1.5
Mannitol	4	4	—	—	—		3.9	3.7	3.7
Glycerine	—	—	1.85	1.8	1.75	1.65	—	—	—
Boric Acid	0.3	—	0.4	0.4	0.4	0.4	0.1	0.3	0.3
Edetate Disodium	0.01	0.01	—	—	—	—	—	0.01	0.01
Edetic Acid	—	—	0.05	0.05	0.05	0.05	—	—	—
Polysorbate 80	0.05	—	0.05	0.05	0.05	0.05	—	0.05	0.05
N-Lauroylsarcosine	—	—	0.03	0.03	0.03	0.03	—	0.03	0.03
Benzalkonium Chloride	—	0.011	0.011	0.011	0.011	0.011	—	0.01	0.01
Benzododecinium Bromide	0.012	—	—	—	—	—	—	—	—
Tromethamine	0.56	0.14	0.39	0.62	0.56	0.94	1.76	1.14	1.44
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

TABLE 4-continued

INGREDIENT	SAMPLE								
	A	B	C	D	E	F	G	H	I
	100	100	100	100	100	100	100	100	100
Gel Strength (G', Pa)	140	128	34	4	2	1	1	2	72

Example 5

Gel Strength Correlation between Xanthan Gum Raw Material and Finished Product

To demonstrate the correlation between the gel strength formed by xanthan gum raw material using the Lysozyme Gel Strength Test and that formed by finished product, the gel strength of Compositions A and B of Example 2 (following steam sterilization) were evaluated. The results are shown below in Table 5.

TABLE 5

Sample	Raw Material G' (Pa)	Composition A G' (Pa)	Composition B G' (Pa)
1	180	114 (n = 23, RSD = 12%)	100 (n = 26; RSD = 10%)
2	104	92 (n = 9; RSD = 12%)	67 (n = 9; RSD = 13%)
3	164	115 (n = 1)	73 (n = 1)
4	85	46 (n = 2)	32 (n = 1)
5	199	100 (n = 2)	104 (n = 2)

Example 6

Calculation of Total Ionic Strength

The ionic strength contributions from the different ions of Compositions A–C of Table 2 were calculated using a pH=6.9 and are shown in Table 6. At this pH, the following charged species (excluding xanthan gum itself) are present in the composition:

1. mannitol-boric acid-tromethamine buffer: monovalent anionic mannitol borate complex adjusted to pH 6.9 with monovalent cation tromethamine. This contributes an ionic strength of about 46 mM to all three compositions.

2. benzododecinium bromide: because the concentration of this ingredient is so small and because the valence is 1 for both the benzododecinium and bromide ions, the ionic strength contribution to each of the three compositions from this is insignificant.

3. timolol maleate: at pH 6.9, timolol maleate would be present as monovalent timolol cations, divalent maleate anions and monovalent maleate anions. The ionic strength contribution of timolol maleate and the amount of tromethamine needed to adjust the pH of timolol maleate to pH 6.9 is approximately 22 mM for position A and 42 mM for Composition B.

TABLE 6

IONS	pKa	% Monovalent at pH 6.9	% Divalent at pH 6.9	A	B	C
Timolol	9.21	99.5		3.9	7.9	0.0
Maleate*	6.33	21.2	78.8	13.0	26.1	0.0
Tromethamine	8.08	93.8		27.8	30.9	23.2

TABLE 6-continued

IONS	pKa	% Monovalent at pH 6.9	% Divalent at pH 6.9	A	B	C
Boric Acid**	5.7–5.85	94.1		22.8	22.8	22.8
Total				67.6	87.7	46.0

*Second pKa

**pKa of boric acid in presence of 3.75 to 4.4 wt. % mannitol.

Example 7

Effect of Ionic Strength on Xanthan Gum's Ability to Gel

The effect of total ionic strength on xanthan gum's ability to gel was evaluated by varying the concentration of NaCl in the 0.6% (w/w) solution of xanthan gum in the Lysozyme Gel Strength Test. Specifically, the Lysozyme Gel Strength Test described in Example 1 was performed five times for the same lot of xanthan gum, but each time the NaCl concentration was different. As a control sample, a 0.6% (w/w) xanthan gum solution (same lot of xanthan gum as in the previous five samples) was tested using the Lysozyme Gel Strength Test (0.5% (w/w) of NaCl), except that it was not mixed with any chicken lysozyme. The results are shown below in Table 7 and in FIG. 4. A 0.7% (w/w) solution of NaCl has an ionic strength of approximately 120 mM [0.5 ((7/58.5×1000)+(7/58.5×1000))=119.6].

TABLE 7

NaCl concentration (w/w)	Elastic Modulus (G', Pa)
0.5	178
0.6	106
0.7	35
0.8	6.3
0.9	2.6
Control	13

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

We claim:

1. An improved ophthalmic composition comprising xanthan gum, wherein the improvement comprises the composition having a total ionic strength of about 120 mM or less and the xanthan gum having an initial bound acetate content of at least about 4% and an initial bound pyruvate content of at least about 2.5%, provided that the composition does not contain locust bean gum.

2. The composition of claim 1 wherein the amount of xanthan gum is from about 0.1 to about 1% (w/w).

3. The composition of claim 1 further comprising an ophthalmic drug.

4. The composition of claim 3 wherein the drug is selected from the group consisting of anti-glaucoma agents; anti-infective agents; non-steroidal and steroidal anti-inflammatory agents; growth factors; immunosuppressant agents; and anti-allergic agents.

5. The composition of claim 4 wherein the drug is selected from the group consisting of timolol; brimonidine; tobramycin; ciprofloxacin; rimexolone; olopatadine; latanoprost; 15-keto-latanoprost; fluprostenol isopropyl ester; isopropyl [2R(1E,3R),3S(4Z),4R]-7-[tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate; and the pharmaceutically acceptable salts thereof.

6. The composition of claim 1 further comprising one or more agents selected from the group consisting of buffering agents; preservatives; tonicity-adjusting agents; surfactants; solubilizing agents; stabilizing agents; comfort-enhancing agents; emollients; pH-adjusting agents; lubricants; and drug carrier substrates.

7. The composition of claim 1 wherein the xanthan gum forms a gel having an elastic modulus (G') of approximately 130 Pa when measured in the Lysozyme Gel Strength Test.

8. The composition of claim 1 wherein the composition has a total ionic strength of about 94 mM or less.

9. The composition of claim 1 wherein the composition comprises tobramycin or a pharmaceutically acceptable salt of tobramycin, a preservative, a pH-adjusting agent, a tonicity adjusting agent, and xanthan gum.

10. The composition of claim 1 wherein the composition comprises timolol or a pharmaceutically acceptable salt of timolol, a preservative, a pH-adjusting agent.

11. The composition of claim 10 wherein the composition comprises timolol maleate, benzododecinium bromide, tromethamine, boric acid, mannitol, and polysorbate 80.

12. The composition of claim 1 wherein the composition is intended for treating dry eye and comprises a pH-adjusting agent and a tonicity adjusting agent.

13. The composition of claim 12 wherein the amount of xanthan gum is 0.4–0.8% (w/w).

* * * * *

United States Patent [19]

Mazuel et al.

[11] **Patent Number: 4,861,760**

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[54] **OPHTHALMOLOGICAL COMPOSITION OF THE TYPE WHICH UNDERGOES LIQUID-GEL PHASE TRANSITION**

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[51] **Int. Cl.**[4] **A61K 31/715**; A61K 31/70

[52] **U.S. Cl.** **514/54**; 514/912; 514/913; 514/915; 514/944; 536/1.1; 536/114; 536/123

[58] **Field of Search** 514/54, 944, 912, 913, 514/915, 954; 536/123, 114, 1.1

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[57] **ABSTRACT**

The present invention relates to a pharmaceutical composition intended for contacting with a physiological liquid characterized in that said composition is intended to be administered as a non-gelled liquid form and is intended to gel in situ, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling in situ under the effect of an increase in the ionic strength of said physiological liquid.

8 Claims, 1 Drawing Sheet

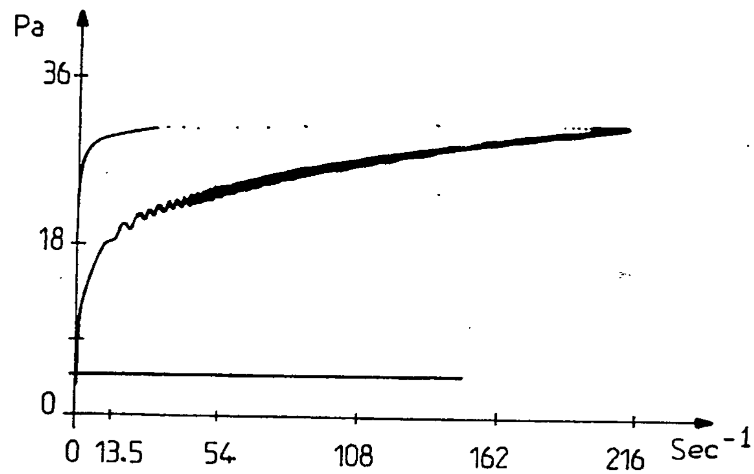

FIG-1

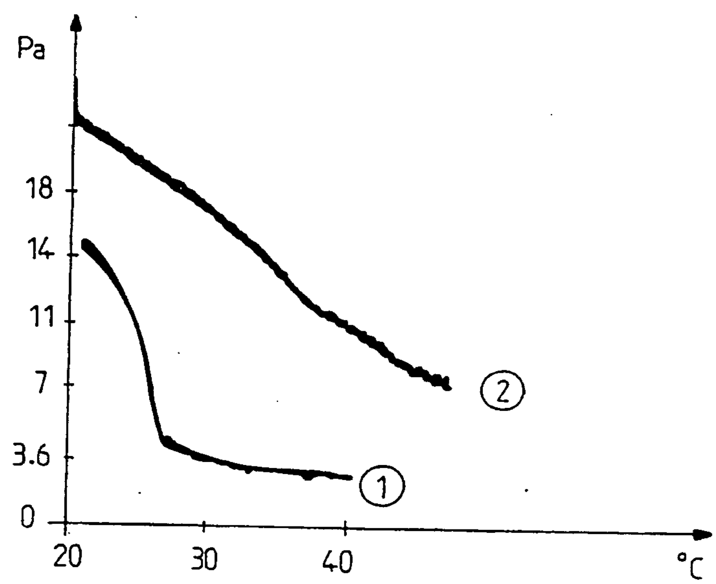

FIG 2

OPHTHALMOLOGICAL COMPOSITION OF THE TYPE WHICH UNDERGOES LIQUID-GEL PHASE TRANSITION

The present invention relates to a pharmaceutical composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength.

The pharmaceutical compositions of the invention are of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength.

They are particularly intended for contacting with physiological liquids. Thus the transition occurs at the contact, as the physiological liquids have a higher tonicity than the one of said compositions.

The compositions of the invention are specially useful for ophtalmic use, but also as injectable form, the formed gel having thus the function of slow-release form, as by intradermic or intramuscular injections, or as galenic form intended for contacting with mucous membranes.

A large percentage of drugs administered to the eye is lost as a result of lacrimal drainage; this applies especially in the case of a liquid formulation. In effect, as a result of this drainage, only a small fraction of the dose administered remains in contact with the cornea for a few minutes, and an even smaller fraction penetrates into the eye.

To overcome this disadvantage, it is known to use viscous solutions, gels, eye ointments or solid eye implants.

Progress has been made in the delivery of drugs by the use of these galenical forms, especially by using the solid implants, by means of which it is possible to reduce greatly the doses of active principle in the formulation while retaining a therapeutic response equivalent to that which would be induced by an eye lotion, the latter, in addition, needing to be administered more frequently.

Some of these implants function by diffusion. Thus, for example, in the "OCUSERT®" system, one weekly application of an oval lens in the conjunctival sac enables an active principle to be delivered by diffusion, but this lens has to be removed after use, which is a source of problems for the patients.

Others function by dissolution, and, in this case, since the implants are either soluble or autodegradable ("LACRISERT®" system), their duration of action is much shorter.

In all cases, the solid implants possess a major disadvantage in that many patients find it difficult to tolerate the introduction into the conjunctival culs-de-sacs of the solid object represented by this implant.

To solve this problem, galenical forms can be used which are liquid at room temperature and assure a semisolid form at human body temperature. Such delivery systems are described in U.S. Pat. No. 4,188,373, which propose the use of "PLURONIC® polyols".

These "PLURONIC® polyols" are thermally gelling polymers in which the polymer concentration is chosen in accordance with the desired liquid-gel transition temperature.

However, with the commercially available "PLURONIC® polymers", it is difficult to obtain a gel of suitable rigidity while maintaining the transition temperature at physiological temperatures, which are of the order of 25° C.–36° C.

Similarly, Canadian Patent No. 1,072,413 describes systems containing a therapeutic or other agent (poloxamer), the gelification temperatures of which are made higher than room temperature by using additives.

The thermally gelling systems have many disadvantages, including the risk of gelling before administration by an increase in the ambient temperature during packaging or storage, for example.

U.S. Pat. No. 4,474,751 of Merck & Co., relates to other systems for delivering drugs based on thermogelification of gels, but these systems require very large amounts of polymers and this is not always well tolerated by the eye.

The present invention relates to a pharmaceutical composition intended for contacting with a physiological liquid characterized in that said composition is intended to be administered as a non-gelled liquid form and is intended to gel in situ, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling in situ under the effect of an increase in the ionic strength of said physiological liquid.

The prefered pharmaceutical composition according to the invention is an ophthalmological composition, the physiological liquid being the lacrimal fluid. Thus, the present invention overcomes these particular problems of administering ophthalmic compositions.

As a matter of fact, the composition, which takes the form of a liquid before its introduction into the eye, undergoes a liquid-gel phase transition, and hence changes from the liquid phase to the gel phase, once it is introduced into the eye, as a result of the ionic strength of the physiological fluid which is in this case, the lacrimal fluid.

This new ophthalmological composition is an amazingly advantageous form for several reasons. In particular, since the presence of lacrimal fluid is required to induce gel formation, any accidental spillage of solution outside of the eye cannot result in gel formation. Furthermore, in contrast to the thermally gelling systems, an increase in the ambient temperature cannot result in the solution gelling during storage.

Also, the polymer used can form a gel at concentrations 10- to 100- fold lower than those used in systems involving thermogelification. It is hence very well tolerated by the eye.

Finally, when these compositions contain a pharmaceutically active substance, such a delivery system makes it possible to achieve great bioavailability of the product, and concentrations of active principle which are sustained with time, advantages of a slow delivery system.

Furthermore, in the case of already gelled or semisolid compositions, it is not possible to administer them by volumetric means, especially when they come from a multi-dose container. To administer these in reproducible quantities, one is then compelled to employ gravimetric means.

The compositions according to the invention have, on the one hand, the advantage of liquid ophthalmic compositions, namely reproducible and accurate dosing, by volumetric means, of the active substance, and on the other hand the advantages known for the systems in rigid or semisolid gel form, relating to the delivery of active substances.

The composition according to the invention consequently has neither the disadvantages of losses of active substances characteristic of simple liquid compositions, nor the unpleasant aspects of solid implant systems, nor finally the difficulties of administration associated with gelled or semi-solid compositions.

The Applicant Company has demonstrated that aqueous polysaccharide solutions, of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, and are especially suitable according to the invention, are solutions of a polysaccharide obtained by fermentation of a microorganism.

Thus, according to the invention, an extracellular anionic heteropolysaccharide elaborated by the bacterium *Pseudomonas elodea* and known by the name gellan gum is preferably used.

This polysaccharide, manufactured by KELCO & CO., is already used as a gelling agent for culture medium and also in food products. The structure of this heteropolysaccharide consists of the following tetrasaccharide repeating unit:

→3)-β-D-Glcp-(1→4)-β-D-GlcpA-(1→4)-β-D-Glcp-(1→4)-α-L-Rhap-(1→

which may, or may not, be partially 0-acetylated on its β-D-glucopyranose (β-D-Glcp) residues.

The preparation of such polysaccharides in native and deacetylated form is described, in particular, in U.S. Pat. Nos. 4,326,053 and 4,326,052 of MERCK & CO., Inc. Rahway N.J., and their structure has been described, in particular, by JANSSON & LINDBERG, Carbohydr. res. 124 (1983) 35-9.

According to the present invention, aqueous solutions containing about 0.1% to about 2.0% by weight of gellan gum, and especially of the product known by the tradename Gelrite®, which is a low acetyl clarified grade of gellan gum, are viscous at low ionic strength but undergo a liquid-gel transition when the ionic strength is increased, and this is the case when this aqueous solution is introduced into the eye.

The rigidity of the gel can be modified by adjusting the polymer concentration.

The gellan gum product not only has the property of changing form the liquid to the solid phase when placed in a medium of higher ionic strength, but it also possesses two advantageous additional properties according to the present invention.

In effect, Gelrite® in aqueous solution is thixotropic (FIG. 1) and thermoplastic (FIG. 2).

These two properties enable its fluidity to be increased by shaking or slightly warming the sample before administration to the eye.

FIG. 1 shows the rheology of a 0.6% aqueous solution of Gelrite® at 20° C. (shear stress (Pa) versus shear rate (Sec^{-1})).

FIG. 2 shows the shear stress (Pa) versus temperature (°C.) behavior [at a constant shear rate of 86 $second^{-1}$] of a 0.6% Gelrite® solution, after a 30% dilution:

(1) in distilled water;

(2) in a simulated tear fluid.

This latter case of FIG. 2 (2) shows the increase in viscosity resulting from the dilution of Gelrite® in a simulated lacrimal fluid.

Thus, the Applicant Company has demonstrated gel formation in a rabbit's eye following a 20 μl instillation of a solution containing 0.4% by weight of Gelrite® deionized water.

The ophthalmic compositions according to the invention can be used as they are in various applications, and, for example, to maintain adequate hydration of the eye (treatment of dry eye syndrome).

Furthermore, it appears that the ophtalmic compositions according to the invention are especially suitable for administering to the eye any pharmaceutically active substance administered for curative and/or diagnostic purposes. Thus, the present invention relates to a pharmaceutical composition which contains at least one pharmaceutically active substance for curative or diagnostic purposes.

By pharmaceutically active substance, there is understood one or more drugs and/or one or more diagnostic agents. Any active substance can be delivered by the compositions according to the invention. The active substance is preferably chosen to be soluble in water, although some active substances show greater solubility than others in the aqueous polysaccharide solutions according to the invention. Furthermore, active substances can be in suspension or in emulsion (e.g. emulsions of oil droplets, complex lipidic materials, liposomes) in the aqueous polysaccharide solutions. Therefore, the present invention relates to ophthalmic compositions containing at least one active substance in solution or suspension or emulsion in the aqueous polysaccharide solution.

The prefered pharmaceutically active substance, used according to the present invention is timolol or one of its derivatives.

Timolol can be used alone or in combination with other pharmaceutically active agents.

The present invention relates to the ophthalmic compositions preferably containing about 0.1% to about 2.0% by weight of the polysaccharide described above, and about 0.001% to about 5% by weight of at least one pharmaceutically active substance.

The quantities relating to the aqueous gellan gum solution make it possible to obtain a suitable gel consistency and to compensate the loss induced by the sterilization procedures used during the process of manufacture of these ophthalmic compositions.

Other additives can also take part in the ophthalmic compositions according to the invention. These are, in particular, other polymers suitable for topical application to the eye, small amounts of acids or bases for adjusting the pH to values suitable for administration to the eye, nonionic tonicity adjusting agents, surfactants, agents for controlling bacterial contamination or, for example, other additives for solubilization or stabilization of the active substance, or any other additive which assist in the formulation.

If necessary, the gel-inducing effect of ionized active substances, for example, which are incorporated in the compositions according to the invention, can be neutralized by adding to the formulation a suitable ion pair-forming agent.

For example, the slight gelling effect induced by adding 0.1 mg/ml of benzalkonium chloride in a Gelrite® solution according to the invention can be eliminated by adding a small amount of acetic acid. The Applicant Company has in addition demonstrated that Gelrite® solutions according to the invention are compatible with other formulation ingredients such as various buffers and potential ion pair-forming agents.

As will emerge in the examples, mannitol can be used in the compositions according to the invention in order

to regulate the tonicity of the medium without changing the gelling properties.

Other tonicity adjusting agents can be used, sorbitol or any sugar for example.

For their administration to the eye, the ophthalmic compositions according to the invention are administered in liquid form, by any conventional means for delivering drops, such as an eye-dropper or, for example, the so called "OCUMETER®" system.

The compositions according to the invention can be administered in the usual manner for eye lotions, in the inferior cul-de-sac of the conjunctiva on the outside of the eye.

By way of example, a drop of liquid composition containing about 25 mg of ophthalmic composition enables about 0.0025 mg to about 1.25 mg of active substance to be administered.

The active substances, or drugs, or diagnostic agents, used in the pharmaceutical compositions according to the invention are preferably suited to the treatment of the disease from which the patient is suffering and/or to the diagnostic method which it is desired to employ.

For example, if the patient is suffering from glaucoma, the active substance chosen in preferably a beta blocker such as timolol or one of its derivatives.

Toxicological studies prove the good tolerability of gellan gums: acute oral toxicity tests in rats show that the lethal dose 50 (LD_{50}) is greater than 5000 mg per kg; acute toxicity tests by inhalation show that exposure of rats for 4 hours to a nominal concentration of 6.09 mg/l does not cause the death of any animal in a group of 10 animals, which indicates that the lethal concentration 50 (LC_{50}) is greater than 6.09 mg/l.

DRAIZE-type eye irritation tests in rabbits show that the product is not regarded as an eye irritant.

When these compositions contain an active substance, the objective of such a system for delivering the active substance is to achieve great bioavailability of the substance and concentrations of this substance which are sustained with time.

The drugs or diagnostic agents which can be administered by means of the ophthalmic compositions according to the invention are, for example:

antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin and sulfonamides:

aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin:

nalidixic acid and its analogs such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogs thereof:

antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogs thereof:

anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac, its salts and its corresponding sulfides, and analogs thereof:

miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivaloylepinephrine, neostigmine, echothiopate iodide, demecarium bromide, carbamoyl choline chloride, methacholine, bethanechol, and analogs thereof:

mydriatics such as atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine, and analogs thereof:

other drugs used in the treatment of conditions and lesions of the eyes such as:

antiglaucoma drugs for example timolol, and especially its maleic salt and R-timolol and a combination of timolol or R-timolol with pilocarpine, as well as many other adrenergic agonists and/or antigonists: epinephrine and an epinephrine complex, or prodrugs such as bitartrate, borate, hydrochloride and dipivefrine derivatives and hyperosmotic agents such as glycerol, mannitol and urea: carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)-thio-5thiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide; and 6-pivaloyloxy-2-benzothiazolesulfonamide

antiparasitic compounds and/or anti-protozoal compounds such as ivermectin, pyrimethamine, trisulfapidimidine, clindamycin and corticosteroid preparations;

compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, and interferon and interferon-inducing agents such as poly I:C;

antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole:

anesthetic agents such as etidocaine cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine:

ophthalmic diagnostic agents, such as:

(a) those used to examine the retina such as sodium fluorescein;

(b) those used to examine the conjunctiva, cornea and lacrimal apparatus, such as fluorescein and rose bengal: and

(c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine:

ophthalmic agents used as adjuncts in surgery, such as alpha-chymotrypsin and hyaluronidase:

chelating agents such as ethylenediaminetetraacetic acid (EDTA) and deferoxamine:

immunosuppressants and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine: and combinations of the compounds mentioned above, such as antibiotics/antiinflammatories combinations such as the combination of neomycin sulfate and dexamethasone sodium phosphate, and combinations concomitantly treating glaucoma, for example a combination of timolol maleate and aceclidine.

Generally, the tears produced by the eye dilute the active substance and very rapidly deplete the dose of active substance administered by conventional liquid solutions.

The compositions containing a polysaccharide in aqueous solution according to the invention, of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, are diluted less rapidly and make it possible to obtain a sustained delivery of the active substance dissolved or suspended

in the composition. (To this end, the total ionic strength of the formulation must be kept as low as possible). This prolonged residence time, permitted by the composition according to the present invention, leads to more effective levels of concentration of active substance in the lacrimal film.

A test which demonstrated the prolonged presence of the active substance after instillation in the eye of a composition according to the invention, and also other characteristics and advantages of the present invention, appear in the Examples and Figures which follow, which illustrate the invention (the percentages being given by weight).

EXAMPLE 1

Simple ophthalmic composition

	Solution 1	Solution 2	Solution 3
Gelrite ®	0.6%	0.6%	0.2%
benzalkonium chloride	0.01%	0.005%	—
mannitol	4%	4%	—
sufficient water to make	100%	100%	100%

EXAMPLE 2

Composition for delivering timolol

	Solution 1	Solution 2	Solution 3
timolol maleate	0.34%	0.65%	0.34%
Gelrite ®	0.6%	0.6%	0.6%
benzalkonium chloride	0.01%	0.01%	—
mannitol	4%	4%	4%
sufficient water to make	100%	100%	100%

EXAMPLE 3

Composition for delivering dexamethasone phosphate

	Solution 1	Solution 2	Solution 3
dexamethasone phosphate	0.1%	0.05%	0.1%
Gelrite ®	0.6%	0.3 %	0.6%
benzalkonium chloride	0.01%	0.01%	0.01%
mannitol	4%	4%	4%
sufficient water to make	100%	100%	100%

EXAMPLE 4

To demonstrate the prolonged presence of the active substance in the eye, after instillation of the active substance incorporated in a composition according to the invention, a comparative test was performed.

The removal of fluorescein from the conjunctival sac of rabbits after an installation of fluorescein solution, either in distilled water or in a vehicle containing 0.6% Gelrite ®, was observed by far UV radiation.

In the eyes treated with the aqueous solution, no fluorescein remains 3 hours after the instillation, whereas in the eyes treated with the vehicle containing the Gelrite ®, fluorescein is still persisting 5 hours after the instillation.

EXAMPLE 5

Composition for delivering timolol

Studies are carried out in vivo to obtain data concerning the timolol bioavailability from the solution 1 of example 2. The concentration of timolol in aqueous humor of non-anaesthetized Albino Rabbits is valued. Single 50 μl Instillations of Gelrite ® Formulations (Example 2 solution 1) and Timoptic ® commercial solutions, each Containing 0.25% of timolol are carried out for a comparison purpose. The Gelrite ® Solutions were Made with 3 Different lots of Gelrite ® Polymers. The obtained results are shown in the following table:

Time after instillation in minutes	Concentration of Timolol in Aqueous Humor in ug/ml ± S.E.M. (N)				
	GELRITE FORMULATION			Average Gelrite	TIMOPTIC
	Lot 001	Lot 002	Lot 003		
30	4.1 ± 0.6 (8)	3.0 ± 0.3 (20)	3.2 ± 0.4 (8)	3.4 ± 0.2 (36)	1.1 ± 0.1 (20)
60	2.3 ± 0.4 (8)	2.9 ± 0.3 (20)	3.0 ± 0.2 (8)	2.7 ± 0.2 (36)	0.9 ± 0.3 (16)
120	1.1 ± 0.2 (4)	1.6 ± 0.2 (16)	1.1 ± 0.1 (8)	1.3 ± 0.03 (28)	0.4 ± 0.05 (8)
180	1.0 ± 0.2 (4)	0.8 ± 0.1 (16)	0.6 ± 0.05 (8)	0.8 ± 0.06 (28)	0.3 ± 0.04 (12)

Note:
S.E.M. = Standard Error of Mean
N = Number of eyes tested

The invention is not limited to the above examples; the compositions of the invention are also useful for their application in all pharmaceutical compositions, which are intended for contacting with the physiological liquids.

Thus, the present invention also concerns the injectable compositions, for intradermic or intramuscular injections, and external topical compositions which are intended for contacting with mucous membranes.

We claim:

1. A liquid aqueous ophthalmological composition comprising 0.1 to 2% by weight of gellan gum which on administration to the eye changes from a liquid to a gel as a result of the ionic strength of the lacrimal fluid.

2. The composition of claim 2 which additionally comprises about 0.001% to 5% by weight of an ophthalmic pharmaceutically-active substance.

3. The composition of claim 2 wherein the pharmaceutically-active substance is selected from the group consisting of an antibacterial substance and an anti-glaucoma drug.

4. The composition of claim 3 wherein the antibacterial substance is norfloxacin and the antiglaucoma drug is timolol maleate or a carbonic anhydrase inhibitor.

5. The composition of claim 1 wherein the gellan gum is Gelrite.

6. The composition of claim 5 which additionally comprises about 0.001% to 5% by weight of an ophthalmic pharmaceutically-active substance.

7. The composition of claim 6 wherein the pharmaceutically-active substance is selected from the group consisting of an antibacterial substance and an antiglaucoma drug.

8. The composition of claim 7 wherein the antibacterial substance is norfloxacin and the antiglaucoma drug is selected from the group consisting of timolol maleate and a carbonic anhydrase inhibitor.

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